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AN INTRODUCTION

TO

PATHOLOGY AND MORBID ANATOMY.

AN

INTRODUCTION

TO

PATHOLOGY AND MORBID ANATOMY.

BY

T. HENRY GREEN, M. D.,

PHYSICIAN TO CHARING CROSS HOSPITAL, AND TO THE HOSPITAL FOR CONSUMPTION AND DISEASES OF THE CHEST, BROMPTON; EXAMINER IN MEDICINE TO THE CONJOINT EXAMINING BOARD FOR ENGLAND; LATE LECTURER ON PATHOLOGY AND MORBID ANATOMY AT CHARING CROSS HOSPITAL MEDICAL SCHOOL.

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PREFACE.

DR. GREEN having asked me to edit this (the seventh) edition of his Text-book of Pathology and Morbid Anatomy, I have subjected it throughout to careful revision, and have, in many places, altered or rewritten portions, even of those chapters which I had revised or written for the sixth edition. Thus I have recast the chapter on Fatty Degeneration, made considerable changes in the accounts of other degenerative processes, rewritten the etiology of Inflammation, made numerous additions to the accounts of the Infective Granulomata, inserted a section upon Rhinoscleroma, and rewritten much of the chapter on the Vegetable Parasites. So far as it goes, I trust that the information given will be found accurate and up to date.

There are, however, several subjects not touched upon, which I think ought to be dealt with in a manual such as this; but lack of time has prevented me from adding more than a chapter upon Fever.

Several new wood-cuts, by Mr. Collings, have been prepared for this edition, and a still larger number of blocks—illustrating chiefly Diseases of Vessels and of the Spinal Cord—have been furnished by the Meisenbach Co. from excellent negatives lent by my friend and colleague, Dr. F. W. Mott.

The book is issued in a larger size and contains a larger number of pages than in the last edition. Much of this increase is due to the use of larger type and to the insertion of the new blocks.

I cannot end without expressing my regret that Dr. Green should have withdrawn his guiding hand from the work. All who have hitherto profited by his knowledge and extensive practical experience, by his skill in grasping important points, and in presenting them shortly yet clearly and connectedly to the student, will realize the difficulty of the position I have been called upon to fill, and may be thereby inclined to deal leniently with some of my many shortcomings.

STANLEY BOYD.

May, 1889.

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PATHOLOGY

AND

MORBID ANATOMY.

INTRODUCTION.

ANATOMY AND HISTOLOGY investigate the naked-eye and microscopic structure of the healthy body; physiology examines the functions of the parts and elements revealed by them, and studies the chemical processes which constitute healthy life. To obtain a knowledge of disease parallel courses must be adopted. In post-mortem examinations we note all naked-eye departures from normal anatomy; next, the microscope is employed to show the finer changes to which these departures are due; and, lastly, we endeavor to find out the causes of the abnormal structure and function which constituted the disease, their mode of action, and the nature and sequence of the disturbances which they produce. We thus get pathological anatomy and histology, and pathology—the physiology of disease.

The guiding principle of modern pathology being that pathology has to deal with no new tissue-cell or function, but simply with disturbances of normal elements and functions, it is obvious that for the purpose of studying disease our acquaintance with the body in health cannot be too intimate. As causes, not products, of disease, new cells (bacteria) and even entire animals (parasitic worms, etc.) are frequently introduced into the tissues.

The complex human organism can be reduced to very simple elements—cells and the intercellular substances to which they give origin. These two elements make up every tissue, the cells being sometimes in excess, as in epidermis, where they seem to be in absolute contact—sometimes the intercellular substance, as in the connective

tissues. It is now universally accepted that the cell is the seat of nutrition and function. Health and disease must be considered as terms referring, not to the body as a whole, but to the cells of which it consists.

Before treating of disease we will say a few words upon the constitution of cells in health, and upon their functions and the conditions under which they are physiologically discharged.

CONSTITUTION OF CELLS.—When Schwann established the analogy between the animal and vegetable cell, the former was held to be constructed, in all cases, upon the same principle as the latter, and to consist of a **cell-wall** enclosing a cavity in which were contained a **nucleus** and **fluid contents** (Fig. 1). But the fact that no cell-wall can be demonstrated in embryonic cells, blood-corpuscles, and the cells of many rapidly-growing new formations led Leydig and Max Schultze to believe that a little mass of matter, enclosing a nucleus, was all that was necessary to constitute a cell. Max Schultze established the identity of the cell-substance with animal sarcode—a contractile substance existing in the lower animals—and showed that it also was capable of spontaneous movement. He called this substance, of which all cell-bodies, animal or vegetable, are, at least at one period of their existence, composed, **protoplasm**, and pointed out that a distinct cell-wall resulted from a retrograde process occurring in its outer layers. Dr. Beale promulgated similar views.

Fig. 1.

Cells from a Cancer, showing cell-wall, cell-contents, nuclei, and nucleoli; the nuclei dividing.

The definition of a cell has been still further modified by the discovery that a nucleus is not essential; for none exists in the cryptogamia and in some of the lowest animal forms. In these exceptional cases the cell consists of a simple mass of protoplasm, but in the higher animals the nucleus is almost constant. The cell-wall is much less so, and must be regarded, in point of vitality, as inferior to the rest of the cell.

Protoplasm is a very complex body, of the molecular constitution of which we are ignorant. It contains a large quantity of water, and its solid residue is largely made up of albuminoid material; but with this there are always associated, apparently in an amalgam-like way, some carbohydrate, fat, and inorganic salts; for they are invis-

ible, yet not in true combination. Some authorities regard the proteid element as alone essential to the manifestation of life. Protoplasm, as seen in the bodies of normal cells, is generally structureless, soft, and viscid, but varying much in fluidity. Granules are frequently present in it, often in one part and not in another, and these probably always differ chemically from true protoplasm. Small cavities, full of fluid, looking like clear spaces, are often seen; they are called **vacuoles,** and may either riddle the cell or one large one may occupy much of its body. They appear, disappear, and change their position.

In highly specialized cells protoplasm has acquired a distinct structure—*e. g.* the fibrillation of muscle and nerve-cells and the striation of many ciliated cells and gland-cells. In many cells, after hardening in chromic acid, a fine network of fibres is seen in the cell-substances—a fact which has led Klein and others to believe that the protoplasm of cell-bodies is really arranged like a sponge, the interstices being occupied by fluid containing granules which are moved about by contractions of the protoplasm. This view explains many phenomena of cell-life; but up to the present time has not been supported by the observation of living cells.[1]

Under certain circumstances protoplasm undergoes metamorphoses into various substances—*e. g.* mucin, globulin, keratin, pepsin and other ferments, glycogen, colloid, and fat—which may form large portions of the bodies of cells. When glycogen and fat arise from a proteid a nitrogenous molecule must also be formed.

This protoplasm is the essential constituent of the **body** of every cell. In comparison with the nucleus the body varies much in size, being sometimes large, sometimes quite insignificant.

The **cell-wall,** when present, is of much firmer consistence than the rest of the body, and seems to be due to some metamorphosis of the protoplasm of the latter.

The **nucleus** is more constant than the body, both in size and form. It is usually spherical or oval, but may be quite rod-shaped; is generally placed near the centre of the cell, and may be single or multiple. It resists destructive reagents more strongly than does the body, and in disease often remains after this has been destroyed; it is stained more deeply by carmine and logwood. Its presence may be concealed by fat, pigment, or other substances in the cell-body. The nucleus does not exist in red blood-corpuscles, and it is doubtful

[1] Schäfer: *Brit. Med. Journ.*, vol. ii., 1881, p. 227.

whether or no the nucleated red blood-corpuscles of the early embryo disappear or are converted into the non-nucleated disks which succeed them. Those formed endogenously in connective-tissue corpuscles in later fœtal and extra-uterine life are apparently never nucleated: they have been likened to chlorophyll-granules. The nucleus of epidermic scales may finally be converted into keratin, and disappear.

The nucleus, which was formerly regarded as a spherical vesicle bounded by a definite membrane which separated the nuclear fluid from the cell-substance, is now known to possess with great constancy the following much more intricate structure: 1, a membrane bounding it externally; 2, a network of fibres, probably contractile, and certainly capable of great changes in closeness and general form; 3, one or more nucleoli, said by some to be only nodal points in the network; 4, a clear, more or less fluid substance which fills the membrane and lies in the meshes of the network. The more solid portions—membrane, network, and nucleoli—are spoken of as nucleoplasm; the less solid, as nuclear matrix. Under Genesis of Cells we shall describe the remarkable changes which occur in nuclei previous to the division of cells.

PHYSIOLOGY OF CELLS.—We will now give a short summary of the normal functions of cells, and of the conditions under which they are physiologically discharged.

A unicellular organism, like the amœba, takes in food, grows, and excretes, performs certain functions, of which motion is the most obvious, and reproduces its like. The whole of this may be regarded as work done, and implies the expenditure of force: and we may be quite sure, although we know nothing of the chemical processes going on in an amœba, that its excreta are simpler compounds than its ingesta, the difference in heat-value between these two sets of compounds representing the force which is available to the organism. The ability to effect these chemical and physical processes, in which the "life" of the animal—as recognizable by us—consists, is inherited, and is spoken of as "**vital activity**" or "**vital energy.**" The possession of this is naturally the first essential to living. The other requirements of the cell are a **sufficient supply of suitable food** and **appropriate surrounding physical conditions**, such as a normal temperature and suitable density of the surrounding fluid.

In man, a multicellular being, the cells vary much in form and in

the results of the chemical actions which they effect. Although retaining more or less independence, varying with the kind of cell, they are bound together for the common good, and each has some special function to perform. Thus there are muscle-cells to produce motion, gland-cells to secrete and excrete, and nerve-cells to control the working of muscle, glands, and perhaps other tissues; certain cells are set apart for reproduction; and, finally, there are the connective tissues to unite and support the other structures, and surface epithelium to protect them. Thus each kind of work done by the one cell of the amœba is in man performed by a group of cells specialized for the purpose. If, then, we recognize the interdependences of the cells in the human organism upon each other, and the differences in their structure and purpose in the economy, all that has been said of the amœba will apply to each cell of the body: all the functions of the amœba are probably present in each cell, but one—*e. g.* contractility of a muscle-cell—is often so highly developed as to be called *the* function of the cell.

Vital Activities.—The **vital energy** of each cell manifests itself in three channels; hence Virchow speaks of the **Nutritive, Functional,** and **Reproductive Activities.** Between the two former there is no line—the existence of one implies that of the other; both are chemical, and may be considered together. **Food** is taken into the body, digested, and absorbed by lacteals and blood-vessels from the intestines; the various excretory organs give off urea, and, in small quantity, other nitrogenous bodies, carbonic acid, and water. Supposing the body to be in **nutritive equilibrium**—neither gaining nor losing weight—the amounts excreted will account for the nitrogen, carbon, and hydrogen taken in as food. Putting aside water, certain salines, and oxygen, which are essential to life, the food-stuffs are albumen, carbohydrates, and fats—the materials of which the body consists. It is evident that a large amount of heat must be set free in the breaking-down of these bodies to the excreta above mentioned; and this is the source of the force by which every act is performed. The blood carries the prepared food-stuffs to the capillaries, where they pass out with the lymph to come into actual contact with the cells—some in solution, others only in suspension. Certain or all of these bodies are now taken up (apparently actively, for albumen will not diffuse from a watery fluid), and become *part of the substance* of a cell, replacing some older material which has been broken down to supply force for assimilation and all other actions

of the cell. This breaking-down of cell-substance consists in the union of it with oxygen obtained from the blood and stored by the tissues in some unknown way. All such oxidation processes are believed to take place *in* the cells, *not* in the blood; and this almost necessitates that all food shall become part of a cell before it is oxidized; it is not oxidized directly. Although the tissues of the body and the food-stuffs have almost the same chemical composition, waste tissue is not repaired by a process of simple replacement from the food, if we except fat: when a fat of the same composition as human fat is contained in the food, it may be stored in the cells without undergoing previous change, but usually some slight addition or subtraction of hydrogen is necessary. It is probable that many changes, both analytical and synthetical, occur in the arrangement of the elements of food-stuffs before they form protoplasm, the real *living* tissue, and force is thus alternately liberated and rendered potential; but this does not affect the main fact that the body ultimately obtains the force equivalent to the difference in heat-value between the ingesta and excreta.

We have enumerated the compounds presented to cells in lymph, and also those which leave the body as the ultimate products of cell-action; but in no instance do we know the connecting links between the end-products. Whilst the ingesta of cells must be tolerably uniform[1] in character, their excreta are probably as various as are the uses of the cells in the body—witness the different compositions of the many secretions and the unequal distribution of the extractives, such as kreatin, xanthin, etc. The breaking down of tissue, or **waste**, which is going on constantly, on the one hand, and the building up or **repair** which in health keeps pace with it, on the other, constitute the **nutritive exchange** of the cell or of the whole body. This process is constantly being disturbed from pathological causes: and, physiologically, formation exceeds waste during the period of growth, but the opposite obtains in old age, when the vital energy of all cells is failing and their functions are imperfectly discharged.

The excreta pass in two directions: into lymph and back into the blood, or out to a mucous or cutaneous surface, whence part may be absorbed—*e. g.* saliva, gastric juice, and part of the bile.

Conditions of Health of a Cell.—That the nutritive exchange

[1] The fluid exuding from the capillaries of different parts presents qualitative and even quantitative difference (Cohnheim).

of the cells of the body may be normal the same conditions must be present as those necessary for the healthy life of an amœba. These were—1, the possession of normal vital activity or ability to effect chemical change; 2, a sufficient supply of food of suitable quality, depending in man upon the circulation and blood constitution; and 3, the presence of appropriate surrounding physical conditions. To these must be added—in the case, at least, of nerves, muscle, and certain gland-cells—4, connection with a healthy nervous centre.

Influence of the Nervous System upon Nutrition.—When motor nerve-fibres are cut off from the ganglion-cells of the anterior cornu, or when sensory are severed from those of the posterior spinal ganglion, they rapidly atrophy, the axis-cylinders being probably long processes of these cells. Section of a motor nerve causes atrophy of the muscles supplied by it, and section of the chorda tympani is followed by wasting of the submaxillary gland. Each of these tissues has an active function to perform, but physiologically this function is never performed except in response to nervous stimulus. Removal of this consequently checks or annuls their nutritive exchange, and deprives them of the afflux of blood which accompanies their action. In the above instances the nervous system undoubtedly exercises a **trophic influence,** though not by means of any special trophic nerves. It is said by some to have the same influence over all the cells of the body; but this is denied by others, who fully allow its power over nerves, muscle, and such glands as secrete physiologically only in response to stimulation of special secretory nerves. The question at issue is, *whether the nervous system influences those chemical changes in which the life of cells, other than gland, muscle, and nerve, consists.* The discussion is carried on mainly with reference to the "non-working cells"—connective tissue and epidermic. Can the nervous system increase the vital energy of a cell and cause it to assimilate more food, to grow and multiply? Can it inhibit the performance of these functions and produce atrophy? Or can it so change the metabolism of cells that their products become irritating and cause inflammation? The question is a very important one, and cannot at present be decided; but the arguments on each side will be given.

In the first place, a general objection has been raised to experiments having for their object to prove the presence of special trophic nerves—viz. that the influence of other kinds of nerves, especially vaso-motor, has not been eliminated. It is necessary to remember

always that after section of the nerves of a limb the part beyond is insensitive, its muscles never contract, the afflux of blood which accompanies their action is lost to the part, and the venous circulation no longer receives help from them. Its vessels at first dilate when the central control is removed, and the part reddens and warms from flow of a larger quantity of blood through it: but soon the general increase of tonus compensatory to the local diminution dies away, the vessels of the part remain dilated, and the flow through them becomes slower than natural; consequently the part is cold and pale or bluish. After a time, however, the local vascular nerves gain power, and a certain amount of tonus, which is easily upset, is restored. These disturbances in the nutritive and physical conditions of a part may explain many changes in it without calling into existence a special set of nerves.

The facts which are held to prove the influence of the nervous system on the nutrition of cells in the non-working tissues are the following: The **fall of the carbonic acid discharge** which occurs when the body is exposed to a high external temperature, and **the increase** which results from under opposite conditions, show that diminished and increased chemical changes share with vaso-motor changes the duty of maintaining an average temperature. It seems most probable that the alterations in metabolic activity are owing to nerve-influence, but it has not been proved that this is exercised on non-working tissues. It has been above stated that the chemical decomposition which gives rise to muscular contraction occurs physiologically only in response to nervous stimuli, and part of the force liberated appears as heat. It is possible that this decomposition may be effected slowly under nerve-influence without causing contraction, force being manifested as heat only. Perhaps this may be one way in which the rise of temperature in fever is caused.

The **diabetes** which results from head injuries and from puncture of the floor of the fourth ventricle seems certainly to be due to a too rapid conversion of glycogen into sugar in the liver-cells; and Foster inclines to the view that this is due to the direct action of nerves on the cells. But others connect the abnormal metabolism with the dilatation of the hepatic arteries and free supply of arterial blood which always result from puncture.

Many **inflammations** of skin, mucous membranes, viscera, bones, and joints are described as due to section or irritation of trophic nerves.

In some cases of hemiplegia (especially from hemorrhage), and occasionally from sabre-wounds of the brain, extremely **acute bedsores** form on the opposite buttock; and similar lesions appear over the sacrum in paraplegia from sudden extensive pathological or traumatic lesions of the cord. They are distinguished from ordinary bedsores by the early date (second or third day) and acuteness of their onset, and the uselessness of the usual precautionary measures. Cohnheim objects to these that they are but differences of degree, and that there is no constancy in their occurrence with apparently similar lesions of any particular part of the cerebro-spinal axis. It certainly is strange that trophic influence should be so marked just at pressure-spots: doubtless the nerve-lesion is merely predisposing. In this class of cases, too, **cystitis** and **pyelitis** may appear at about the same time as the bedsores; and Charcot thinks that these inflammations are due to irritation of trophic nerves; but as exceedingly foul urine, which invariably contains organisms, is noted before or with the onset of cystitis, others believe that the latter is due to organisms introduced from without (often by a septic catheter), or from within through the kidneys, which render the urine extremely irritant by putrefaction. Similar cases occasionally occur after the passage of a few catheters in cases of enlarged prostate.

Trigeminal Keratitis, etc.—Intracranial section of the fifth nerve causes cloudiness of the cornea in twenty-four hours, and often destructive panophthalmitis; at the same time ulcers appear on insensitive parts of the mucous membranes of mouth and nose. The ulcers in the mouth are probably due to unheeded injuries from the teeth, but ulcers from the nose cannot thus be accounted for.

It is said that the keratitis can be prevented by most carefully protecting the eye from injury with the still sensitive ear. **Ulcers on the foot,** often progressive, after section of the sciatic are similarly accounted for.

Pneumonia after section of the vagi is due to entry of food, etc. through the insensitive glottis, but this will not account for pneumonia or pulmonary apoplexy on the side opposite to a cerebral hemorrhage. **Acute fatty degeneration of the heart** may follow section of the vagi: the *modus operandi* is unknown.

Erythema, Urticaria, Pemphigus, and especially **Herpes,** may appear in the distribution of nerves which are the seats of some irritant lesion, as after fractured spine, in locomotor ataxy and other

scleroses of the cord, compression by an aneurism or tumor, or inflammation of the Gasserian or a posterior spinal ganglion. The nerves supplying the area of the rash have been found in a state of neuritis.

The rapid variations of erythemata and urticaria certainly seem to point to a nervous origin, but do they involve more than an acute vaso-constrictor paralysis?

Glossy Skin (Paget).—In some cases of irritative lesion of the sensory nerves of limbs (*e. g.* from gun-shot) the skin becomes smooth, shiny, hairless, sometimes hyperæmic, sometimes œdematous, often superficially inflamed or the seat of sores like chilblains; at the same time the part is often the seat of intense neuralgia. Less severe symptoms, but obviously similar, are seen after simple section, and may be due to disturbances of circulation and temperature and to anæsthesia.

Pigmentation.—More or less symmetrical patches of leucoderma and melanoderma may occur all over the body, with more or less anæsthesia; pallor with anæsthesia and localized grayness of hair may occur in neuralgia of branches of the fifth. The color of the hair may to some extent return between the attacks. Cases have been recorded in which the hair has within a short time of a fright become gray.

Serous Synovitis and **Arthritis**, with rapid, painless, and great erosion of the articular ends of the bones, may occur in cases of hemiplegia and ataxia, and are supposed to be due to involvement of the cells of the anterior cornu by progressive sclerosis. The causal relationship between the nervous disease and the peripheral lesion cannot be yet said to be proven.

Atrophy of Parts cut off from the Nervous System.—Muscle and certain glands have been treated of above. In the case of muscle, it is to be noted that if it is regularly exercised by the galvanic current, atrophy may long be postponed. In a paralyzed limb all tissues ultimately waste; so also does the face when paralysis of the facial is not recovered from. This is due to impaired blood-supply, for it occurs in limbs which are simply kept at rest. Atrophy of the cock's comb and turkey's wattles results from section of their nerves, and is perhaps to be similarly explained. In cases of progressive atrophy of half the face there may be nothing to guide one to the nervous system as the cause: there may be no subjective symptoms, and sensation and motion remain normal. If due to nerv-

ous influence, this atrophy would seem to favor the existence of trophic nerves.

Hypertrophy of bone may follow section of the sciatic in young animals, and is inflammatory; for it never occurs unless large ulcers form, extending to the bone, and even causing necrosis. Hypertrophy of the rabbit's ear after section of its nerves has been said to occur; but many observers have failed to produce it, or have, at most, seen thickening of epidermis and hair upon it.

There is, then, no reliable evidence of the existence of special trophic nerves, and no convincing proof of the interference of the nervous system in the chemical processes of cells which perform no special function. That these processes may go on undisturbed in the absence of nervous influence is shown by the perfect development of other parts which is found in anencephalous and amyelous embryos, by the growth of transplanted epithelium and connective tissues, and by the union of completely severed parts. At the same time, as we cannot offer a perfect explanation of many of the above-mentioned cases, we cannot say that the nervous system has no direct influence upon connective tissues and epidermic cells: it seems most probable that it has. In the present state of our knowledge, however, it is dangerous to explain anything by such an influence; it is better to leave it doubtful.

The Reproductive Activity.—Having now dealt with the Nutritive and Functional Activities, we must consider the Reproductive. In early life, at least, all cells possess the power of reproducing their like, and in the majority this power is retained, although it may not be exercised physiologically, up to advanced age. Cessation of growth does not imply absence of ability to grow, for growth seems to cease when the supply of nutritive material to a part is only just sufficient to maintain its *status quo*. This is seen in a hair, which will not grow beyond a certain length: cut it short, and growth at once begins again, the supply of food being greater than the now shortened hair requires for simple nutrition. To cause cells which are capable of multiplying to do so, the supply of food must be increased. Thus, exercise of a muscle causes increased blood-supply and consequent growth; but increased blood-supply to a working tissue, without exercise, will not have this effect. It is different with non-working tissues. The hyperæmia round an ulcer of the skin, or even chronic congestion and œdema of a part, causes thickening of epidermis and connective tissues, and nothing is commoner than new

formation of bone round a carious focus. For this effect the increased supply must be very frequent or long continued.

A non-working tissue apparently tends to grow also when the resistance offered to its growth by neighboring tissues is diminished: of this we shall find many examples in cirrhotic processes and in the etiology of malignancy (Cohnheim).

The cells of the body inherit very different amounts of vital energy. The cells of the thymus are soon exhausted, those of the epiphyseal cartilages later, and of the generative organs later still. In all cases, probably, the reproductive activity is the first of the vital manifestations to suffer; then the functional and nutritive. Inability to perform such chemical changes as are necessary to remove effete material and to repair waste is natural in old age; death, which may be termed natural, then results from "senile decay."

GENESIS OF CELLS.—Virchow's dictum—*Omnis cellula e cellula*—is admitted now by all but a few. Probably every nucleus also is derived from a pre-existing nucleus.

Multiplication of cells takes place by **simple division.** The cell divides generally into two, and the change is preceded by remarkable appearances in the nucleus. According to Flemming, the process of "karyokinesis" may be very briefly described as follows (Fig. 2): First, the nuclear membrane disappears; then the **resting** nuclear network (*a*) becomes much finer and closer, like a ravelled **skein**; then again more open, and, if not already so, the cell becomes round (*b*). There seems to be now only one fibre forming the nuclear network, which next assumes the form of a **rosette** or **wreath** (*c*) round a clear central space, whilst a clear central zone intervenes externally between the network and the cell-substance proper. By division of the external bends of the fibre and approximation of the apices of the V's, so as to obliterate the central space, a star-form, **aster** (*d*), is produced. The fibres at this stage often become finer and more numerous by longitudinal division from their free ends toward the centre. Instead of radiating from the centre, they now become first parallel, and then convergent toward two opposite points—the poles—of the original nucleus, so that the fibres now form two sets of V's, with their angles away from the equator—**equatorial stage** (*e*). A clear equatorial line appears, and widens (*f*), as one set of V-fibres retreats from the other division. From each group the nucleus of a daughter-cell is formed by passing

through—in reverse order—all the stages above mentioned (*g* and *h*), until the resting stage is reached. Meanwhile, the protoplasm

FIG. 2.

Forms assumed by a Nucleus in Dividing: *a*, resting nucleus; *b*, skein-form, open stage; *c*, wreath-form; *d*, aster, or star-form; *e*, equatorial stage of division; *f*, separation more advanced; *g* and *h*, star and wreath forms of daughter-nuclei. (Reduced from Flemming's drawings in the *Arch. f. Mik. Anat.*)

of the cell-body collects round each nucleus, and by the time these have assumed the wreath-form its division is complete. The daughter-cells, at first small, grow, and may themselves shortly divide; and thus multiplication may be very rapid.

The nucleus may divide several times without any division of the cell-body occurring, but the latter increases continuously in size. This is said to be one way in which "giant" or "myeloid" cells—large, irregular, multinucleated masses of protoplasm, found in the marrow of growing bone, in chronic inflammations, and in some new growths—may be produced (Fig. 3).

FIG. 3.

A Multinucleated Cell: from the lung in a case of chronic phthisis, showing the large number of nuclei with bright nucleoli. × 400.

Finally, it remains to be pointed out that cells originating from one embryonic layer give rise to cells of a kind formed normally from another layer. **Epiblast** forms nervous tissue and the epithelium of sense-organs, of the ventricles of the brain and central canal of the cord, of the skin, mouth, and lower end of rectum. **Hypoblast** forms the epithelium of the alimentary canal and of all glands connected with it. The

Mesoblast forms the epithelium of the kidney, testicle, and ovary, the epithelium of vessels and serous membranes, all the connective tissues, blood, and muscular tissue.

Disease.

Having thus dealt with the structure and functions of cells in health, we may now turn our attention to disease. The functions of an organ are really the functions of the cells of which it consists: if all these act normally, we say that the organ is sound; and when all the functions of every organ and tissue in the body are normally performed, we describe the individual as being in perfect health. A very little experience shows that physiological functions vary within certain, perhaps rather wide, limits, the perfect well-being of the individual being maintained. Consequently our standard of **Health** is no rigid one; its maximum and minimum are widely separated, and the latter shades off imperceptibly into **Disease.**

It will be inferred from the above that the **definition of disease** is *abnormal performance of function by one or more organs or tissues.* This applies to "disease" as a general term; but when we speak of a specific disease, as rheumatism or syphilis, the cause of such disease—that to which the peculiar disturbances of function or structure which distinguish the disease in question from all others are due—is implied in the word. The same or indistinguishable disturbances of function and structure may be produced by several causes: it is the more or less constant grouping or sequence of symptoms or lesions which establishes distinct diseases.

It is worthy of note also that the *maintenance of a physiological maximum or minimum* must be regarded as pathological. For example, a man out of training will eliminate much more urea than normal on the first day of a walking-tour, but the average daily elimination for the whole tour will not vary from normal. If, however, the man were to go on excreting the maximum quantity of the first day, his state would be one of disease.

VARIETIES OF DISEASE.—The complete healthy life of a cell consists in the perfect performance of all its functions. For this three things are necessary: 1st, that which it inherits—its vital energy—must be normal; 2d, it must be supplied with sufficient suitable food; 3d, its surrounding physical conditions must be nor-

mal. Failure in any one of these will lead to disease, and two great classes of diseased conditions are at once evident—**inherited**, due to abnormality of the first; **acquired**, due to abnormality of the second and third.

Inherited Disease.—The tendency to inherited disease either exists in the ovum at the commencement of development or is acquired by the ovum in fertilization: later than this any tendency appearing is obviously acquired. As in normal development certain organs manifest their inherited tendencies many years after birth—*e. g.* the development and atrophy of the female generative system at puberty and menopause, the appearance and union of epiphyses—so inherited tendencies to disease (although, like normal tendencies, they may appear *in utero*) may not show themselves until late in life, as is the case in cancer of the breast or uterus. It is possible that in many cases the same unrecognized conditions which induced in a parent the morbid tendency handed down continue to act on the offspring until—with or without some obvious exciting cause—the disease becomes evident. We cannot say when this tendency to disease begins: it may have been slowly gaining strength for generations. The fact that no progenitor had the disease in question, if he or she lived well past the age at which such disease usually manifests itself, shows simply that the causes had not acted long enough or with sufficient energy to produce it. It is important to recognize that even inherited disease has its starting-point in conditions external to the cells of the body.

With regard to the actual mode in which disease is inherited, it is in some cases probable that the poison, the actual cause of the disease, is present in the ovum or spermatozoon, as has been shown to be the case in the silkworm disease (Pasteur). But how disease and tendencies to diseases which are not due to any specific poison are handed down we know no more than we do how it is that children inherit the features of their parents.

Often, no actual disease is inherited, but the power of resistance of certain tissues against the causes of certain diseases (*e. g.* tubercle) is more or less impaired; or the tissues degenerate early, especially in the fatty or calcareous manner, so that many members of a family may die at about the same age from fatty heart or apoplexy.

Acquired Disease.—Starting with an organism or part the vital energy of which is normal, disease, if it occur, must necessarily be

the result of external conditions; the supply of food is faulty either in quantity or quality, or the physical conditions to which the part is or has been exposed are unsuitable. It is difficult to separate the two. If the blood-supply to a part is abnormal in quantity, the temperature of the part will be changed; if a portion of the body is mechanically injured, its blood-supply becomes abnormal; if a poison excites fever, the cells are exposed to a higher temperature than normal: a *circulus vitiosus* is established. Disease may be acquired even during intra-uterine life—*e. g.* acute specifics, syphilis.

General and Local Disease.—Any change in external conditions acting upon a unicellular organism would probably affect every particle of its substance and modify all its functions; all its diseases would therefore be **general**. But multiplication of cells and specialization of functions enable abnormal conditions to act upon certain groups of cells and to disturb their functions without affecting (primarily at least) those of other groups. We thus get **local** disease; and the great majority of diseases belong to this class. Perhaps, indeed, we may say that every disease is primarily localized in a tissue or organ, the blood being counted as a tissue of the connective type of which the intercellular substance is fluid.

Structural, Organic, and Functional Disease.—A disease is localized in an organ or tissue during life by its symptoms and by its physical signs: and after death we as a rule find the localization justified by the discovery in the part of some constant structural change. This is **structural** disease. In a large number of cases, however, there are no physical signs, only symptoms (epilepsy), or the physical signs are secondary to some primary abnormality of function in one or more organs (gout, diabetes). There may then be doubt as to the organ or system at fault; and often this doubt can be settled only by the discovery of a constant structural change associated with the symptoms in question. Diseases in which no such change has been found are classed as **Functional**, the belief being that in them the functions of certain cells are abnormally performed, without any structural change. Modern research has greatly diminished the number of functional diseases; but it is almost certain that a very large number of the slighter ailments are due to faults in the chemical changes (the metabolism) effected by cells. **Organic** disease probably, in the first place, meant that pathologists had been enabled to localize a disease in an organ by means of structural

change in it. It has now come to be used as synonymous with "structural."

ETIOLOGY OF DISEASE.—The causes of disease are divided into two classes—**Predisposing** and **Exciting.**

Predisposing Causes.—Any agency which tends to cause departure from the physiological state of the whole body or of a part must be regarded as predisposing to disease—*e. g.* privation, frequent irritation. Many such agencies, when acting more strongly, become excitants of disease—*i. e.* cause the step outside the physiological limit to be taken. If to ciliated cells, detached from the body and acting strongly under the microscope, a hot iron be approached, its first effect will be to increase or stimulate their action; but if the iron be kept near them long or be brought closer, their action slows and ceases. If now the iron be removed at once, the cilia will after a period of quiescence begin slowly to work—one here, one there, then all—and may finally recover completely. This was an experiment of Lister, as also was that of showing the resolution of inflammatory stasis in the amputated web of a frog. They illustrate a point of fundamental importance in pathology—*the inherent power of every cell to recover after injury.* They show for the elements what every one knows of the whole—namely, that, *cæteris paribus*, a strong man will recover from a disease which would be fatal to a weakly one. It is certain, too, that the "life" of cells resists the action of injurious agencies, and that this power of resistance varies in the cases of different tissues—*e. g.* the rabbit's ear resists the effects of anæmia much longer than a knuckle of its intestine—and also in different individuals. Thus, it is a common observation that certain people who have not suffered from the acute specifics tend those ill of these diseases without themselves catching them, whilst others, again, fall victims to them, one after another, though not specially exposed. Such power of resisting certain causes of disease does not imply ability to resist others of a different nature, nor does it necessarily go with muscular strength. It varies at different times in the same individual.

The following predisposing causes are generally considered:

Age.—Special treatises have been written on diseases of childhood and on diseases of old age, showing that there are peculiarities with regard to disease at these periods of life. The special liabilities of childhood are to some extent explained by supposing that the

power of resisting injury which all cells possess is not fully developed until adult age; those of old age, by the fact that the vital powers are wearing out and degeneration occurring.

Sex.—The organs special to the sexes render each liable to special diseases. That women are the special victims of hysteria is probably due to the fact that for generations it has not been considered unwomanly for a woman to display feelings which it has always been the object of men to conceal. But we cannot explain the special liability of women to endemic and exophthalmic goitre and myxœdema, nor their comparative immunity from Addison's disease, ataxy, and general paralysis.

Heredity.—It has already been stated that feeble vital power, without actual disease, may be the heritage of the body or of one of its parts. It may be noted further that, like physiological and personal peculiarities, disease—*e. g.* gout—sometimes skips one or more generations (*atavism*). In other cases, as in hæmophilia, the disease appears generally in the males only, although the females may, without themselves manifesting it, transmit it to their offspring. Disease in the father is more likely to be transmitted to sons, in the mother to daughters.

The diseases which most obviously "run in families" are functional nervous disorders, as hysteria, neuralgia, epilepsy, insanity, and they are more or less interchangeable; carcinoma, especially of the breast and uterus; some simple growths, especially if multiple (lipomata, osteomata, papillomata); gout and tubercular disease.

Exciting Causes.—These may be ranged under the headings of **Abnormal Food-supply** and **Abnormal Physical Conditions**; it may be necessary to add, *Altered Nerve-influence*, but we do not as yet know sufficient of it.

Abnormal Food-supply.—This may be due to errors in the circulation or in the composition of the blood. It may result from hyperæmia or anæmia; from all abnormalities in blood-constitution, whether due to faults in its formation or purification or to the introduction of poisons from without.

Abnormal Physical Conditions.—These include injuries from any one of the physical forces, applied either from without, or, so to speak, from within; the results of mechanical obstacles to discharge of function or of contents—*e. g.* stricture of a duct or orifice, strangulation of gut, pressure, and the mechanical effects of parasites.

EFFECTS OF PREVIOUS DISEASE.—Some diseases, when once acquired, tend to recur again and again. This may be because the tissue affected is at the onset incapable of normal resistance, or because, having once been injured by the disease, it does not recover its pristine state. Sir J. Paget points out how exactly the form and structure of a scar are preserved through years—almost as exactly as are those of normal parts—but, on the whole, it tends to be obliterated. He thinks that this maintenance of the parts in the state to which they have been brought by the injury accounts for their yielding more and more easily each time they are exposed to the action of the same cause. Catarrhal inflammations of mucous membranes, rheumatism, and facial erysipelas are familiar examples of diseases which tend to recur.

On the other hand, there are several diseases which are said to be "protective against themselves." An individual who has had smallpox is, for a time at least, not liable to the disease. This Sir J. Simon explains by supposing that the effect of the disease upon the blood-forming organs is so to modify them that they no longer produce the pabulum necessary for the growth of the smallpox poison. If smallpox be caught a second time, he regards it as a proof that the blood-forming organs have returned to the normal, in accordance with the law above mentioned—that injured tissues tend to recover. Upon this view there would be present in the body of an individual predisposed to the various diseases which are protective against themselves a substance to serve as pabulum for each disease; which seems unlikely; further, nothing is known of such substances. It has been suggested that the growth of the specific poisons of a disease produces some substance which is incompatible with the life of the virus—like the carbolic acid and cressol of putrefaction, the alcohol of fermentation; but it is hard to believe that such substances would persist for long periods in the body. So we have no satisfactory explanation of **acquired immunity**. In connection with the subject we must remember that inoculation with the poisons of syphilis, vaccinia, or variola is without evident effect so soon as the lesions of these diseases are declared—*i. e.* at a time when the same poisons are actively growing in the body. Again, the acquired immunity is conferred by vaccination with the modified poisons of various diseases.

In connection with acquired immunity we may mention the state of the tissues in **inherited immunity**, which is probably the same

as that to which they are brought in acquired immunity. The best examples in man are—instances in which individuals resist the virus of a specific disease in spite of frequent and prolonged exposure to it—*e. g.* a fever nurse may not have had scarlatina, and may never catch it: no negro is liable to yellow fever. It may be that inherited immunity is due simply to the handing down to offspring of the immunity acquired by ancestors by exposure to the poison and often by attacks of the disease: for races which are not yet immune to certain acute fevers (like measles), and which are frequently exposed to them, suffer much less severely than people among whom the disease rarely appears. The complete immunity of the negro to yellow fever is generally accounted for by supposing that only those (speaking roughly) who could resist the disease would live to have children, and that the immunity would be strengthened by union of the immune.

Certain other diseases, again, seem to modify very deeply the functions of the body. Many years after these diseases it is found that illnesses which seem at first sight to have nothing to do with them yield only to the treatment proper for the original malady. Such are malarial fever, syphilis, gout. The poisons of the first two are probably still latent in the body: as to gout, we know too little of its essential nature to speak definitely of the way in which its influence is exercised.

MODES OF EXTENSION OF DISEASE.—**Primary** disease of an organ or tissue is frequently followed by **secondary** disease of other parts. This may happen in several ways:

1. **By direct spread of a morbid process,** as when inflammation extends from skin to subcutaneous tissue or cancer of the mamma involves skin.

2. **By the carriage of causes of disease from a primary focus to parts at a distance** by the lymphatics or by the blood-vessels, as in embolism, of the most varied substances.

3. **Mechanically,** by so-called "*back-telling.*" Thus stricture of the urethra causes hypertrophy of the bladder to overcome the obstacle to the outflow of urine, or dilatation of the bladder if its efforts are futile. In either case the difficulty of entry of urine into the bladder is increased, and the ureters, pelves, and kidneys dilate. Interstitial nephritis results from the pressure, the renal functions are imperfectly performed, and this is detrimental to the

organism at large. The succession of changes which result from mitral incompetence is another familiar example of this mode of extension of disease.

4. **Failure of any Part to do its Share of Work in the Economy.**—The result will depend upon the completeness with which its defection can be compensated. If the work can be done by other parts, as can that of a sweat or sebaceous gland, nothing is noticed; but after extirpation of a kidney which was doing work a time of danger from diminished excretion of urinary products has to be gone through, the other kidney being at first unequal to the double duty. Failure of the cardiac or of the respiratory function will cause death, there being no power of compensation.

TERMINATIONS OF DISEASE.—The possible terminations of disease are *recovery*, or return of the part to the discharge of its normal functions; *partial recovery;* and *death*, or complete cessation of function. Certain diseases can scarcely be said to have a termination; when once established they remain stationary.

It will be useful here to give a list of the morbid processes to which all organs are more or less liable:

The results of mechanical or physical injury.
Displacement.
Hemorrhage.
* * *
Developmental errors.
* * *
Anæmia.
Hyperæmia.
Œdema.
Inflammation.
Atrophy.
Infiltration.
Metamorphosis.
Necrosis.
Regeneration.
Hypertrophy.
Tumor-formation.
* * *
Lodgment of parasites.
* * *
Stricture and its consequences may occur in every duct or canal, and calculi may develop in connection with all such.

CHAPTER I.

NUTRITION ARRESTED.

Necrosis.

The absolute and permanent arrest in a part of the ability to perform function constitutes necrosis, gangrene, or local death.

ETIOLOGY.—Whatever arrests the supply of nutritive material to a part or destroys the vital activity of its cellular elements may cause its death.

A. The supply of nutritive material may be interfered with by—

1. **Obstruction to the Arteries.**—This is a common cause of necrosis. The obstruction may be caused by compression, by ligature, tumor, etc., by rupture, thrombosis, or embolism, or by disease of the arterial coats. If the obstruction be complete and a collateral circulation cannot be established, death of the part quickly ensues.

2. **Obstruction in the Capillaries.**—Obstruction here is often the result of pressure upon or stretching of the vessels. This may take place from the accumulation of inflammatory products, hemorrhage, or from the pressure exercised by new growths. The resulting obstruction to the capillary circulation causes the death of the immediately adjacent tissues. As examples of necrosis from this cause may be mentioned that of the superficial layers of the bone which so frequently results from periostitis, owing to the compression of the capillaries between the bone and the periosteum; the sloughing of tendons in whitlows before they are opened; and the formation of ordinary bed-sores. When inflammation causes gangrene, it is ultimately by the production of stasis, leading to death of the tissues from malnutrition and coagulation of blood in their capillaries. Whenever necrosis of a tissue occurs, the blood coagulates in its capillaries, and thus hemorrhage from gangrenous parts is prevented.

3. **Obstruction in the Veins.**—Obstruction to the return of blood by the veins must be so complete in order to arrest nutrition that it is in itself rarely a cause of necrosis. It is when associated with cardiac weakness or obstruction in the arteries that it constitutes

an important agent in producing this result; for then the force necessary to drive the blood on through the much-narrowed venous channel is quite inadequate. This is seen after ligature of a main artery and its vein, and in accidental injury of the vein during the operation of ligature of a large artery, especially in the thigh; also in constriction of a part by a bandage not tight enough to occlude the arteries.

4. **Diminished Cardiac Power.**—This is never independently a cause of necrosis. In cases, however, of excessive general debility or disease of the cardiac substance, the consequent diminution in the contractile power of the heart materially aids the foregoing causes in producing a fatal blood-stasis. The arrest of the circulation in "senile gangrene," and that which so often occurs in the tissues of the back in adynamic fevers and in chronic exhausting diseases, is in part the result of diminished cardiac power. This arrest in the last-named conditions is usually determined by some injurious irritation of the tissue—in other words, it is a part of an inflammatory process.

5. **Inflammation.**—As a cause of necrosis, inflammation belongs partly to Group A and partly to Group B. The effect of the inflammatory process is to impede or arrest the circulation, and to impair the vitality of the affected part, and the intensity of the process may be so great as to cause coagulation in the capillaries and death of the tissues. (See "Inflammation.") When a strangulated or invaginated piece of gut is released and the circulation is re-established, severe inflammation, perhaps leading to gangrene, frequently ensues. Cohnheim's experiment of tying off a rabbit's ear has been repeated. It is of practical importance to note that inflammation sets in only on re-establishment of the circulation—*i. e.* when the gut is returned to the peritoneum; there is none whilst it is in the sac. A much-contused and lacerated part may ultimately be killed by the pressure of the effusion from its injured vessels still further impeding the flow through them. Certain inflammations have a special tendency to terminate in necrosis, as diphtheria, carbuncle, noma, "hospital gangrene," and spreading traumatic gangrene. In these conditions the intensity of the injury to the tissues is probably due to the action of minute organisms. In all cases the more impaired the nutrition of the part which becomes the seat of an inflammatory process, the more likely is this to cause its death.

B. Destruction of the vital activity of the cellular elements may be caused by—

Physical and Chemical Agencies.—A part may be completely disorganized and lose its vitality as the result of external violence, great heat, or cold. Many corrosive chemicals, as acids and caustic alkalies, destroy the life of cells. Putrid urine or foul secretions from wounds are intensely irritant, sometimes directly destroying the cells like a caustic. As mentioned in the last paragraph, organisms other than those of putrefaction have a similar effect. These physical and chemical causes frequently produce necrosis by exciting, in the first place, acute inflammation.

These are the several causes of necrosis, but it must be borne in mind that the process is often complex, and due to the combined influence of two or more of them. The liability to necrosis will greatly depend also upon *the power of the tissues to resist injury.* This varies probably in different individuals, and certainly in different tissues in the same individual—intestine, for example, being much less resistant to injury than skin. Conditions which lead to the death of a part in which the circulation was already impeded or the vitality of the cellular elements impaired produce no such effect where such local weakness does not obtain. This is well exemplified by the necrosis of the tissues of the back from pressure which so often occurs in conditions of debility; by varicose ulcers of the legs; by the gangrene of the extremities which sometimes results from the long-continued ingestion of ergot; and especially by senile gangrene.

THE CHARACTERS OF THE DEAD PARTS.—These vary according as the part (1) dries or (2) remains moist and putrefies. These two varieties are spoken of as **Dry** and **Moist Gangrene.**

Dry Gangrene or Mummification.—The conditions favorable to the occurrence of this are—causation of the necrosis by interference with the supply of blood to the part, the veins and lymphatics being left free; such position of the part as shall favor the return of fluid by veins and lymphatics; slow progress of the gangrene; removal of the epidermis, which much impedes evaporation; free exposure to a current of cool or hot dry air; and the predominance in the part of such tissues as naturally contain but little fluid—bone, cartilage, and tendon. Under such circumstances the part, which is pale, slowly shrivels, becoming brown or black, and beyond the drying its tissues undergo little change. Dry gangrene often results from embolism, from slowly-progressing arterial thrombosis, and from the prolonged administration of ergot of rye.

Moist Gangrene.—Under opposite circumstances—where, from an acute inflammation or from venous obstruction combined with a weak arterial supply—a part consisting largely of muscle and other soft structures becomes rapidly gangrenous, it is gorged with an albuminous fluid full of breaking-down red blood-corpuscles. The hæmoglobin of these forms a red solution which soaks into and stains all the tissues. The limb is much swollen, of purplish color, and often studded with bullæ of blood-stained fluid. If such a part is exposed to warm, moist air, septic bacteria quickly enter through the skin, multiply rapidly in the highly putrescible fluid, and generate by their action gases—chiefly sulphuretted hydrogen, ammonia, nitrogen, and carbonic acid—which give rise to the emphysematous crackling so often associated with gangrene. The tissues soften and liquefy, the whole part becomes exceedingly offensive, and its tissues change in color from reddish to brownish or greenish black. For putrefaction to occur it is absolutely essential that septic bacteria be admitted to the part; consequently, such changes are met with chiefly in external parts or internal organs to which air has free access. When the life of an internal organ or part is destroyed, as by infarction, but bacteria are not admitted to it, its tissues undergo a series of degenerative fatty changes known as **necrobiosis.**

COURSE.—Gangrene may be **circumscribed** or **spreading.** The course varies chiefly with the cause, but the **resistance of the tissues,** depending upon their vital energy and blood-supply, must always be taken into account, for causes which have little effect on healthy tissues lead to sloughing in the aged, the diabetic, albuminuric, or intemperate.

With regard to the first factor—circumscribed gangrene implies a circumscribed cause. This form is exemplified by the death of tissue resulting from mechanical violence, the actual cautery, complete stoppage of the circulation, etc. On the other hand, spreading gangrene necessitates a cause which spreads before it. Thus, gangrene from arterial thrombosis often spreads, but slowly and with a well-defined margin. But the typical spreading gangrenes are those due to inflammation, in which, probably, the action of organisms on the fluids of the part constantly provides fresh quantities of the irritant.

When the process becomes circumscribed the dead tissue—**sphacelus** or **slough**—acts as an irritant to the adjacent living structures, causing more or less inflammation of them. If the slough is aseptic

the inflammation is slight, leading merely to the formation of a layer of connective tissue round the dead mass, by which it becomes encapsuled. This occurs especially in internal parts, and is best illustrated by the fate of simple infarcts. When thus encapsuled the dead part ceases to irritate; it becomes decolorized, fatty, infiltrated with small round cells which absorb the fatty detritus, and is ultimately converted into a small fibrous scar, which may calcify.

When the slough is superficial it generally putrefies and becomes strongly irritant; but mummification will minimize this. The inflammation of living tissue round the now limited slough is spoken of as the **line of demarcation.** Exudation and migration occur freely into a narrow zone of *living tissue* surrounding the edges and base of the slough; fibres and all firm connections between the living and dead tissues are softened and eaten through; and, finally, the slough is cast off when this process is complete by suppuration occurring along the line of demarcation. If the whole thickness of a limb dies, the stump left by casting off the sphacelus will be conical, for the soft parts retract somewhat and the bone separates lower down. The less vascular a tissue, the longer is the time occupied in its erosion—*e. g.* fascia, tendon, bone. After removal of the slough an ulcerated surface is left. If the dead mass be deeply seated, and suppuration occur about it, fistulæ form, leading from it to the surface, through which it may ultimately be cast off. This is seen in necrosis of bone.

Senile Gangrene.

This is a form of necrosis which affects especially the lower extremities of old people, and is the result of several of those etiological conditions which have already been enumerated.

The most important element in the production of senile gangrene is the presence of atheromatous or calcareous changes in the arteries in the limb, which greatly diminish their elasticity and calibre and proportionately impair the circulation in and nutrition of the part. This is shown by the coldness of feet, cramps, and other abnormal sensations so often experienced by the patient for some time before the gangrene sets in. The slowing of the circulation is usually much increased by simultaneous atrophy or degeneration of the muscular substance of the heart itself. The prolonged contact of the blood with an abnormal vessel-wall thus brought about is sometimes sufficient to cause the formation of a thrombus in the artery, which

slowly spreads until it may extend from the foot to the groin. Gangrene begins in one or more toes and also extends slowly. It is surprisingly limited; thus, the whole foot may not be gangrenous where the thrombus extends into the popliteal artery. In other cases embolism with superadded thrombosis may be the starting-point, a chalky plate or a parietal thrombus being swept from a large into a smaller artery. Finally, the gangrene may be inflammatory, due to some very slight injury, such as a slight abrasion of the foot, the cutting of a corn, or excess of heat or cold acting upon the undernourished vessels and tissues.

Post-mortem Changes.

The changes which always occur in tissues after death must now be considered more particularly. First, with regard to the blood. This fluid undergoes the earliest and most rapid change. The hæmoglobin escapes from the red corpuscles, partly by exudation and partly by the destruction of the corpuscles themselves, and, dissolved in the liquor sanguinis, permeates the surrounding tissues. The corpuscles are ultimately completely annihilated, nothing remaining but a few minute granules. The staining of the tissues with hæmoglobin is commonly known as **post-mortem staining,** and the appearances it presents are very characteristic. The lining membrane of the heart and blood-vessels, being in immediate contact with the blood after death, are the parts principally affected. The dissolved hæmoglobin soaks through the superficial vein-walls, and they become marked out on the surface by livid red bands. The staining is of a uniform pinkish-red color, thus differing from the punctiform and stratiform redness of hyperæmia, from which it must be carefully distinguished. The amount of staining is in proportion to the rapidity with which decomposition has taken place and to the amount of blood contained in the part at the time of death. Marked staining of the endocardium and great vessels soon after death is a sign of septicæmia.

Post-mortem Discoloration must be distinguished from this. It is a purplish color more or less marked in dependent parts which are not pressed upon, and is due to the gravitation of fluid blood into the vessels of these parts. It disappears if the body be turned over.

In muscle the arrest of nutrition is accompanied by a state of rigidity known as the **Rigor Mortis.** This is a peculiar condition

of the muscles observed in almost all bodies after death, in which they become firm and somewhat shortened, as though in a state of chronic contraction. It comes on as soon as the muscles have lost their irritability—*i. e.* their capability of responding to artificial stimulation; in other words, as soon as the nutritive processes have completely ceased. The time of its appearance will therefore depend upon the state of nutrition of the muscles at the time of death; the more healthy and vigorous this is, the longer it is before the nutritive processes completely cease, and consequently the longer it is before the rigor mortis supervenes. The length of its duration and its intensity are in direct proportion to the lateness of its appearance. In people, for example, who are in perfect health and die suddenly, as from accident, the rigor mortis does not usually come on until from ten to twenty-four hours after death; it is very marked, and often lasts two or three days. In those, on the other hand, who die from exhausting disease, as from chronic phthisis or the adynamic fevers, in which the nutrition of the muscles becomes much impaired, the rigor mortis appears very soon, sometimes as early as ten minutes after death; it is very slight, and may pass off in less than an hour. It has been said that in cases of death from poisoning by carbolic acid and sulphuretted hydrogen, from lightning, and from some of the severer forms of the adynamic fevers the rigor mortis is entirely absent. It is doubtful, however, if this is the case, as the rigor mortis has probably escaped observation, owing to its early supervention and rapid disappearance. As soon as the rigor mortis has passed off decomposition of the muscular tissue commences.

With regard to the nature of the change, Kühne and others have shown that it is really owing to the coagulation of the albuminous substance of the muscle—myosin. The myosin, fluid during life, coagulates when nutrition has ceased, the coagulation being attended by the liberation of a free acid. Thus are produced the firmness, hardness, and opacity of the muscle characteristic of rigor mortis. These disappear as soon as decomposition commences; the transverse striation of the fibres becomes indistinct, and gives place to irregular rows of granules and fat-molecules; the muscle softens, its sarcolemma is destroyed, and ultimately nothing remains but a soft structureless débris. This change occurs not only in muscle: in the cells of other tissues a similar coagulation of the protoplasm takes place on the cessation of the nutritive processes.

Respecting the *post-mortem* changes in other tissues—protoplasm generally not only coagulates, but tends to become finely granular after death. It sometimes increases in bulk, so that the cells look swollen, and in nucleated cells the nucleus often shrinks or entirely disappears. The cells ultimately break up into molecules of various sizes. In adipose tissue the cells diminish in size, owing to the escape of the fluid fat, which diffuses itself throughout the surrounding structures. The fibres of connective tissue swell up, become opaque, and ultimately liquefy. In nerve-fibres the white substance of Schwann coagulates and collects into small drops (myelin) within the neurilemma. Cartilage, bone, and hair resist the putrefactive process longer than any of the tissues, and are at least altered by it.

CHAPTER II.

NUTRITION IMPAIRED.

INTRODUCTION.—It was shown in the preceding chapter that permanent arrest of nutrition in a part causes cessation of function—*i. e.* death. We must now consider morbid processes in which nutrition is more or less impaired, and proportionate diminution of vital energy the characteristic consequence. Nutrition may be impaired in two ways: in *quantity*, so that waste comes to be in excess of repair; or in *quality*, either the food or the metabolism of the cell being abnormal. Excess of waste over repair leads simply to **atrophy**, or simple diminution in size of a part or of the whole body, whence results impairment of its functional powers. Alteration in the quality of the food or in the chemistry of the cell, on the other hand, *may* lead to **degeneration** of the cell-contents; some abnormal substance appears in the tissues, formed by metamorphosis of the cell-protoplasm or deposited in the cells by the blood and not consumed. This, again, causes more or less impairment of the functions of the degenerate elements. Both atrophy and degeneration must therefore be regarded as stages toward death, and in both cases the impairment of nutrition not uncommonly becomes so extreme that it amounts at certain spots to arrest and consequent death of the most affected cells.

Several abnormal substances may appear in the tissues as results of their degeneration, and according as these substances are believed

to be derived from the cell-protoplasm itself or to be merely deposits from the blood, the degenerative processes are divided into two groups: the **metamorphoses** or **degenerations** proper and the **infiltrations.** They differ essentially. The cell-protoplasm in the **metamorphoses** being transformed, at first partially then entirely, into a new material, function is proportionally and ultimately completely arrested, and finally degeneration of the stroma often leads to annihilation of structure. In the **infiltrations** the new material is not derived from the cell-protoplasm, but is deposited from the blood; there is an infiltration of a new substance. This is rarely followed by destruction of the histological elements or by softening of the intercellular substance; hence the structure of the tissue is much less altered than in the metamorphoses, and function is usually much less interfered with.

The **metamorphoses** are—fatty, mucoid, colloid, and probably albuminoid. The **infiltrations** are—fatty, calcareous, and pigmentary.

Atrophy.

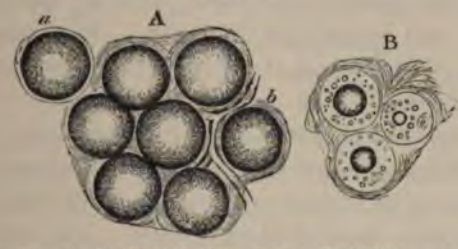
DEFINITION and **VARIETIES.**—Atrophy must be carefully distinguished from arrested development. It is a *decrease* in the amount of a tissue, owing to diminution either in *size* (**simple atrophy**) or *number* (**numerical atrophy**) of the histological elements of which it is composed. It is attended by loss of weight and impairment of function. The two varieties, simple and numerical, are often associated, the latter being an advanced stage of the former.

Atrophy may be **general,** affecting to a greater or less extent all the organs and tissues of the body, or **local,** and limited to particular parts. In general wasting the stress falls at first upon the subcutaneous adipose tissue; then upon fat in other situations, as around viscera and in the omentum; then upon the muscles and glandular organs; and lastly and least on the osseous and nervous structures.

MICROSCOPIC APPEARANCES.—**Simple atrophy** is the most common condition met with in atrophy, and may affect all tissues, as is well shown in ordinary emaciation. Thus adipose tissue is merely common connective tissue, many cells of which are distended with fat. When a person emaciates the fat is gradually removed from the cells, which diminish in size, and the fat which completely filled them may be reduced to a few isolated drops; it is usually partially replaced by serous fluid, the cell-wall and nucleus often become dis

tinctly visible (Fig. 4), and multiplication of the nucleus is often observed (*atrophic proliferation*). This example, though usually given, is not a good one, inasmuch as the diminution in size of the cells is due to the absorption of a substance with which they have been *infiltrated*—which is not essential to their well-being—whilst the protoplasm, at first at all events, is not affected. The cells of all glands may truly atrophy; they become smaller, being often finely granular from the presence of molecular fat, and shrinking of the whole organ

FIG. 4.



Adipose Tissue: A, normal; B, atrophic, from a case of phthisis; a, a single fat-cell, with cell-wall, nucleus, and drop of fat. × 300. (Virchow.)

results. Muscular tissue also may atrophy by simple diminution in the size of its primitive fasciculi; and here, as in adipose tissue, atrophic proliferation of the muscle-nuclei seems to be common.

In **simple atrophy** the shrunken cells are still capable of recovery; hence, all that is necessary for restitution of the tissue is diminution of waste or increase of repair, according as one or other is faulty.

Numerical atrophy is often an advanced stage of simple atrophy. The elements not only diminish in size, but some actually perish, as is well seen in advanced atrophies of muscle; then restitution is possible only by the production of new elements, whereas in **simple atrophy** repair can be effected without new formation. In certain tissues—as the spleen, lymphatic glands, and skin—in which growth occurs by addition of new elements, and not by enlargement of pre-existing cells, atrophy is probably always due mainly to numerical loss.

Although atrophy in its strict signification consists simply in a diminution in size or in number of the component elements of a tissue, it *is rarely a perfectly simple process*, but is usually associated with more or less **fatty degeneration.** This indicates fault in the chemical processes of the cells. Probably, when the nutrition of a part is so much interfered with as to cause it to atrophy, those portions of its

cells which should be combined with oxygen and rendered soluble remain; fatty degeneration is the natural fate of protoplasm under such conditions. It is possible, too, that an atrophying tissue would not store sufficient oxygen for its use. It will be seen subsequently that fatty degeneration arises from causes similar to those which produce atrophy itself.

PHYSICAL CHARACTERS.—The naked-eye recognition of atrophy is often difficult. Atrophied organs are *usually* diminished in weight and size, contain less blood, and are drier, paler, more fibrous-looking, and firmer than in health. The great criterion is diminution in weight and size of an organ; but these vary considerably in health, especially with the weight and size of the whole body; moreover, they may be less than natural from incomplete development. Again, accumulation of blood and serosity in an organ may bring its weight and size up to or above the average, although its essential tissue is considerably diminished in amount. The same fallacy may arise from overgrowth of the fibrous stroma of an organ.

All the tissues of which an organ consists may waste simultaneously, but the term "atrophy" implies, primarily and chiefly, wasting of its characteristic cells as opposed to the stroma. The vessels and nerves of course share in the wasting process. The fibrous constituents are the last to atrophy; and this fact, together with the diminished blood-supply, accounts for the pallor, dryness, toughness, and fibrous appearance above mentioned as usual in atrophied organs. Not uncommonly, as the higher cells shrink and disappear, the connective tissue of the organ *increases*—as in the secondary scleroses of the cord—and it may become the seat of fat-infiltration, as in pseudo-hypertrophic paralysis. This tendency to take advantage of the obvious weakness of a contiguous tissue is perhaps to be explained by Cohnheim's theory of the "physiological resistance" offered by one tissue against invasion of its territory by another. (See Introduction to "Tumors.")

ETIOLOGY.—Atrophy of the whole body or of a part is sure evidence that the total or local nutritive exchange is disturbed, so that waste exceeds repair: this is the *immediate cause of all atrophies.* Repair may be deficient because of insufficient supply of food or because of inability on the part of the tissues to use the food supplied. The circumstances which excite excessive waste in individual cells are but

little understood. It is convenient to speak of general atrophy as distinct from local.

General Atrophy may be caused by—

1. **Deficient Supply of Nutritive Material.**—Whatever interferes with the supply of nutritive material to the tissues will be followed by their atrophy. Deficient supply of food; obstruction to the passage of food into the stomach or intestines, as in stricture of the œsophagus or pylorus; the malassimilation which results from the various conditions giving rise to dyspepsia; interference with the absorption of the chyle from obstruction of the thoracic duct or disease of the mesenteric glands, constituting the so-called "tabes mesenterica,"—may all in this manner be causes of general atrophy.

2. **Excessive Waste.**—All conditions attended by the loss of large quantities of nutritive material may be causes of general atrophy—*e. g.* continuous hemorrhages; profuse and long-continued suppuration from chronic bone-disease or empyema; diarrhœa, or the excretion of large quantities of albumen or sugar in Bright's disease or diabetes. The waste from increased tissue-change accompanying acute febrile diseases must also be included under this head.

3. **Impaired Vital Activity.**—This constitutes an important element in the production of the atrophy of old age—**senile atrophy.** As life advances the ability of the elements to perform those chemical processes which are necessary to prepare and assimilate food to compensate for waste diminishes; hence they gradually atrophy, and ultimately all manifestations of their vitality may cease.

Although general atrophy may thus be referred to one of the foregoing causes, it is rarely of such simple etiology, but is due to the combined influence of two or more of them. The atrophy associated with pulmonary phthisis, for example, results partly from loss of nutritive material in profuse expectoration and diarrhœa, partly from deficient supply consequent upon imperfect oxidation of the blood and interference with assimilation, which is so often caused by structural changes in the stomach and intestines, and partly from the increased tissue-change of fever. In senile atrophy, again, in addition to the general diminution of nutritive activity there is frequently some condition of the digestive organs interfering with assimilation which materially aids in producing the ultimate result. Increased tissue-waste, loss of appetite, and interference with assimilation all help to produce the atrophy which accompanies fever.

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LOCAL ATROPHY.—In local atrophy it is often very difficult to discover which factor in the nutritive exchange is at fault.

1. **Deficient Supply of Nutritive Material.**—The effect of diminishing the blood-supply to a part will vary with the diminution from slight atrophy to death.

Diminished supply of arterial blood is a common cause of atrophy (*passive*), and may be brought about in various ways: (1) By obstruction of the supplying vessels before they enter a part; thus atrophy of the testis has resulted from pressure of an abdominal aneurism on its artery, and wasting of the proximal fragment of a long bone may follow its fracture above the point of entry of the nutrient artery. (2) Pressure may be *continuously and uniformly* exercised upon a part so as not to constrict the veins specially; thus atrophy, even of bones, results from pressure of aneurisms and tumors, deep fissures in solid organs from pressure of band-like adhesions, atrophy of the kidney from obstruction in the urinary passages, and, rarely, wasting of a testis from pressure of old hæmatoceles or hydroceles. (3) Pressure may be developed within the capsule of an organ by the appearance of some new growth or inflammatory effusion, especially that of small round cells going on to the formation of young, strongly contractile connective tissue. The effect of this is seen in granular contracted kidney, cirrhosis of the liver, and all "sclerosing" processes. In groups (2) and (3) (**pressure atrophies**) the constant pressure acts also directly on the cells of the part and impairs their powers.

2. **Diminished Functional Activity.**—This is a convenient *clinical* group, many examples occurring both physiologically and pathologically. But diminished function is never more than the remote cause of atrophy, the immediate being either *deficient supply of food or impaired vital energy.*

Diminished functional activity of a part implies that the chemical processes in its cells are less active than normal; such cells require less food. How the needs of each tissue are made known to the blood-forming organs is not understood; but the supply is, as a rule, speedily adapted to any variation in the demand. Consequently, working tissues will, soon after they have ceased to perform their functions, receive only sufficient material for those chemical processes which do still go on in them. This is insufficient to maintain the mass of protoplasm required to do the full work of the tissue; so some of it atrophies.

After birth those parts which are no longer required in the altered

circulation gradually atrophy. The umbilical arteries and vein become thrombosed up to their first branches, and shrink to a fibrous cord as the clots organize—just like any other vessel cut across or tied. But this does not explain the closure of the ductus venous or d. arteriosus, in which the conditions are not favorable to thrombosis. Obliteration of these vessels can at present be spoken of simply as a developmental fact, comparable to closure of the foramen ovale. The Wolffian body disappears as the kidneys develop and the thymus wastes in the second year; these perhaps are examples of atrophy of organs owing to the development of others better fitted to do the work—illustrating, as it were, the converse of the law that when an organ atrophies or is removed correlated organs hypertrophy and take on its function. (See "Compensatory Hypertrophy.")

Muscles rendered inactive by ankylosis or chronic disease of joints, by splints, or by paralysis from disease or injury *above* the anterior cornual cells with which they are connected, atrophy. When the muscles of a part waste, all its other tissues—nerves, vessels, bones, etc.—suffer ultimately from impaired blood-supply. Thus, in part at least, we may explain wasting of the bone in a stump or limb long kept at rest; the absence of that intermittent pressure which it is the function of bones to bear is probably a secondary cause—at all events, increased strain causes hypertrophy of a bone. After removal of the distal part of a limb the main artery and branches supplying it become smaller and thinner. The rectum dwindles after colotomy to a scarcely pervious cord; in addition to the loss of the muscular action passage of feces over the mucous membrane no doubt acts as a stimulant to its vessels, and, as it is never distended, the tissues adapt themselves to the empty condition. Atrophy of the optic nerve follows on removal of the eyeball.

The female generative apparatus atrophies at from forty-five to fifty, the male somewhat later; the spleen and whole lymphatic system waste after middle life: probably in these cases the vital energy of the cells of the parts concerned is exhausted about the times mentioned, and diminished function is the result, not the cause. They would then be of the same nature as "senile decay."

Trophoneuroses.—But when a muscle is cut off from its connection with its cells in the anterior cornu, or when these cells are destroyed or seriously injured, an atrophy of the muscle, much more rapid than that resulting from diminished functional activity, sets in. In the latter case those changes which nervous stimuli alone can phys-

iologically excite (p. 24) probably go on, but in the former they are completely arrested. Examples of this atrophy are afforded by the acute bulbar and spinal paralysis of adults, infantile paralysis, some cases of progressive muscular atrophy, neuritis from any cause, rupture, contusion, or section of a nerve. Certain glands (salivary, testis?) waste on section of their nerves. Nerves cut off from their ganglion-cells (of which they are long processes) also degenerate rapidly and waste. In all these cases the interstitial connective tissue increases, and often becomes loaded with fat as the higher tissue disappears.

3. **Excessive Functional Activity.**—This may, quite exceptionally, be a cause of atrophy—*e. g.* of testis. (See "Hypertrophy of Muscle.")

Atrophy of Bone.

Atrophy must be carefully distinguished from arrested development, which is very common as a result of infantile paralysis or of rickets, inflammation, or of injury leading to early ossification of an epiphysis. A limb is often stunted, and one form of microcephaly is due to premature ossification of the cartilage between the basi-sphenoid and basi-occipital.

Atrophy always causes diminution in the weight, less often also in the size, of a bone; it is usually accompanied by more or less fatty degeneration. Diminution in weight only (**eccentric atrophy**) is usually a *senile change* of general distribution, but specially marked in the neck of the femur and in women, rendering them liable to fracture of the cervix femoris from slight violence. All spaces are enlarged at the expense of their walls—the bone is "rarefied," light, brittle, and fatty; its shape may alter under strain—*e. g.* the cervix femoris becomes more horizontal from birth to adult age.

Diminution in size as well as in weight (**concentric atrophy**) results from the above changes plus absorption beneath the periosteum; the medullary canal shrinks with the external circumference. This is the form met with especially in the long bones in cases of long-standing ankylosis, dislocation, or paralysis, the cause being diminished food-supply due to disuse. Constant pressure is another cause, the hard palate gradually disappearing before plugs inserted into clefts and perforations.

Pulmonary Vesicular Emphysema.

This appears to be a proper place to describe the changes in the lungs in emphysema, as the chief is atrophy of the interalveolar septa.

DEFINITION.—Emphysema consists essentially in a **permanent** enlargement of the infundibula and air-cells due to atrophy of the intervening septa; it should be distinguished from the acute over-distension often seen, especially in children, after death from bronchitis, pertussis, etc.

VARIETIES.—Two are described: 1. Hypertrophous or "large-lunged" emphysema—by far the most important, and always indicated when the term "emphysema" alone is used; 2. Atrophous, small-lunged or senile emphysema.

1. **Hypertrophous Emphysema.**—The lungs are enlarged, sometimes so much that they actually cross in the mid-line in front, obliterate the superficial cardiac dulness, project markedly into the neck, and push down the diaphragm; they collapse but slightly when the chest is opened, and their usually sharp edges (in front and round the base) are pale, thick, round, and more or less irregular from the protrusion of soft, pale, rounded swellings; similar swellings are frequent toward the diaphragm; the tongue-like piece of the left lung below the notch is often extremely swollen, and the lungs may bear distinct grooves corresponding to the ribs. Everywhere, in advanced cases, the air-cells are seen through the pleura with abnormal distinctness, but the apices and sharp edges are first and chiefly affected, spaces of some size being here met with. Abnormal pigmentation is usual. The lungs feel much like a down pillow, and crepitate little. On section, emphysematous parts are pale from anæmia and dry, and they collapse excessively when large spaces are present in the part cut.

Microscopic investigation shows that the dilatation commences in the infundibula, and extends thence into the alveoli opening into it; the interalveolar septa atrophy and ultimately become perforated centrally, their elastic fibres yielding and then disappearing; the pulmonary capillaries are greatly stretched, become thrombosed, and then likewise vanish. The apertures in the interalveolar septa enlarge, and, later, others form between the infundibula, and thus

are develeped irregular cavities which may rarely be as large as a filbert. The largest are situate in the pale, rounded, bleb-like swellings. Fatty degeneration of the alveolar epithelium is commonly present, and is probably secondary to vascular disturbance.

The communications between the pulmonary and bronchial vessels become compensatorily dilated. The connective tissue around the smaller bronchi may be increased as the result of bronchitis.

Hypertrophy or dilatation of the right ventricle frequently results from the obstruction to the pulmonary circulation, any marked dilatation being accompanied by the venous congestion of cardiac failure. The thorax becomes barrel-shaped—almost fixed in a position of full inspiration.

2. **Atrophous Emphysema** occurs usually in thin old people who seem to be undergoing general atrophy. The lungs during life may leave the heart unduly exposed; when the thorax is opened they collapse excessively, falling together "like an inflated bag of wet paper" (Jenner). They are excessively pigmented, and their apices and borders, even after collapse has occurred, usually show appearances like those in the large-lunged variety, and due to similar naked-eye and microscopic changes. In this form, apparently, the elastic tissue is not so generally affected as in the large-lunged variety.

ETIOLOGY.—It is obvious that the causes must either (1) increase the interalveolar pressure, or (2) diminish the resistance of the alveolar walls.

1. Pressure in the air-cells will be increased by violent expiratory efforts with closed glottis, as in coughing; violent muscular efforts during which the glottis is closed and the thorax distended; blowing wind instruments, etc. The least supported parts of the lung suffer most (*expiratory theory* of Jenner). **Primary emphysema** seems due chiefly to causes such as these.

2. The resistance of the alveolar walls may be diminished (*a*) by removal of part of their natural external support, or (*b*) by changes in themselves.

a. When part of a lung fails to expand from collapse, compression, consolidation, etc., inspiration tends more than usually to produce a vacuum in the pleura around about this—*i. e.* the negative pressure in the pleura is increased; the pressure of the atmosphere in the neighboring air-containing cells consequently expands them exces-

sively. When a whole lung fails to expand, the other stretches over toward it, and the mediastinal viscera are displaced in the same direction (**vicarious** or **secondary emphysema**).

b. Weakening of the alveolar walls: *α.* Senile atrophy and loss of elasticity—the most important element in the causation of atrophous emphysema.

β. Atrophy from stretching and obliteration of blood-vessels caused by their over-distension from increased interalveolar pressure.

γ. Inherited weakness (for emphysema may run in families), or weakness due to some interference with their nutrition from mode of life or other causes.

It was shown in the preceding chapter that permanent arrest of nutrition in a part is followed by cessation of function—*i. e.* by death. We must now consider the effects of interference with nutrition falling short of arrest—of diminished blood-supply and assimilation.

CHAPTER III.

FATTY DEGENERATION.

THIS term is here used collectively to cover all cases of abnormal accumulation of fat in the tissues, but it is frequently employed as synonymous with "fatty metamorphosis" and as opposed to "fatty infiltration."

The abnormal accumulation of fat in the tissues may result from either infiltration or metamorphosis (see p. 46)—two essentially different processes as regards causes, nature, and effects. Both occur physiologically.

FATTY INFILTRATION.

In fatty infiltration, fat brought by the blood is taken up and deposited in the substance of certain cells—viz. those of the connective tissue of certain parts (especially subcutaneous and subserous), of the medulla of limb-bones, and to a less extent of the liver, which thus serve, physiologically, as reservoirs of fat. It is impossible to

draw any line between normal and pathological fatty infiltration so long as only cell-groups which are physiologically liable to this infiltration are affected; *e. g.* the subcutaneous fat and the fat normally present in middle-aged adults along the coronary vessels varies much in amount consistently with perfect health. But when the fat spreads widely over the heart-surface it becomes abnormal; and the evidence of disease is much stronger when fat appears between the muscular fibres in cells which, normally, contain no fat. The tendency to morbid fatty infiltration may be **general** (*obesity*) or **local.**

CAUSES.—It may be stated generally that, whenever oxidizable material is present in the blood in excess of the amount required for the supply of force and maintenance of heat of the body, there is a tendency to the deposit (storage) of fat, first in regions in which it is normally present, and then in parts which usually contain none. For this, fat itself need not be present in excess in the food; the presence of carbohydrates in quantity sufficient to satisfy the wants of the organism will protect fat from oxidation. But it would seem that there are factors in the process of fattening other than the relation of **food-supply** to **oxidation,** for nothing is more certain than that a tendency to obesity or to leanness runs in families, and it is notorious that some very stout people are small eaters and active, whilst many thin subjects are just the reverse. Cohnheim has, it is true, advanced the hypothesis that in the former oxidation is naturally slow and imperfect, but we know of no experimental facts in support of the view.

With regard to the sources of fat deposited in the body—the foodstuffs whence it is derived—many views are still held. It appears possible that some **fat** may be absorbed and deposited without change in the tissues when the food contains fat similar in composition to that of the human body; when this is not the case, if any fat of the food is stored in the body it must somewhere undergo the usually slight change (*e. g.* the removal of 2H) necessary to assimilate it to human fat, for under ordinary circumstances the cells will not take up from the blood fats which are not normal in them. The term "infiltration," which implies passiveness on the part of the cell, is therefore probably incorrect in the present instance.

It is believed by most that fat is not formed directly from **carbohydrates,** but that these are burnt and "protect" material from

which fat can be formed; there are, however, many facts in favor of the opposite view.

It is thought that the chief source of fat deposited in the tissues is the **proteids** of the food. These are said to be absorbed and split into a nitrogenous and a non-nitrogenous molecule, from the latter of which fat is formed, and stored if not required.

1. It would appear, therefore, that **excess of the diet** over the wants of the body, particularly if the excess be in hydrocarbons or carbohydrates, is one great cause of fattening. To prevent fattening the diet should be moderate, not only as regards fats and carbohydrates, but also as regards proteids; it is probably best to cut all down proportionately. The taking of alcohol, particularly of malt liquors and sweet wines, should be forbidden.

2. With regard to the second great cause—**diminished oxidation**—this may result, for the body generally, from sedentary and luxurious habits, ease of mind and body, high external temperature, destruction of much lung-tissue by chronic disease, or reduction of the oxygen-carrying power of the blood owing to diminution of red corpuscles or of their hæmoglobin. The fat contained in a normal diet may, under

FIG. 5.

Fatty Infiltration of Connective Tissue, showing the accumulation of fat within the cells. × 300 (Rindfleisch).

such circumstances, be incompletely oxidized. Locally, oxidation may be diminished by slow circulation or the circulation of deoxidized blood through a part—conditions which normally obtain in the liver and in parts thrown out of work; *e. g.* muscle placed at rest. Excess of fat may sometimes be present in the fluids around certain cells—*e. g.* the liver-cells after a meal containing much fat, and the connective-tissue cells and wander-cells near a focus of fatty degeneration.

MICROSCOPIC CHANGES.—Cells undergoing fatty infiltration are seen to contain droplets of oil—very small at first, but usually distinct droplets—which run together, push the cell-nucleus aside, and distend the cell-protoplasm until it may form but a delicate capsule to the fat (Fig. 6). As the fat is added to the previous cell-contents, the cell is obviously larger in proportion to the amount of fat it contains.

NAKED-EYE CHANGES.—A fattily infiltrated organ is consequently more or less swollen, and sharp edges tend to become thick and rounded; it is more or less pale and yellowish on account of anæmia (from increased intracapsular pressure) and the presence of fat; it is doughy and inelastic, and both receives and retains an impression from the pressure of a finger; it is softer than natural. But, except mechanically, the fat does not hinder the protoplasm of the organ from discharging its functions: ultimately, however, pressure upon the cells proper may become so severe that they fail to get sufficient nourishment, undergo fatty metamorphosis, and atrophy. The knife used to cut a fatty organ is greasy, and may show distinct oil-drops on the blade.

Fig. 6.

Liver-cells in Various Stages of Fatty Infiltration. × 300 (Rindfleisch).

SEATS.—The cells most commonly affected to a morbid extent are those physiologically liable to the process—viz. connective-tissue cells and liver-cells: with regard to the former, it is to be noted that, normally, the cells of the interstitial connective tissue of working organs (muscles, nerves, and glands) are not infiltrated, but may become so, especially if in any way the activity of the organ, and the consequent afflux of arterial blood, are arrested. **In obesity**—the commonest result of morbid fatty infiltration—the subcutaneous and subperitoneal connective tissue suffer earliest and most, the infiltration spreading later to the interstitial connective tissue of organs in which oxidation is more active. The process in connective tissue needs no description beyond that given above ("Microscopic Changes"), illustrated by Figs. 5 and 7.

Fatty Infiltration of Muscle.

In muscle, fatty infiltration is common as a morbid process. The *cells in the connective tissue* which surrounds the fasciculi of the muscle become filled with fat; and this development of fat *between* the muscular fasciculi (Fig. 7) must not be confounded with degeneration of the fibres themselves. The interstitial fat varies in amount. In some cases single rows of fat-cells alternate with rows of muscular fasciculi; at other times the accumulation is less regular, more existing between some fibres than between others: in all but the most advanced cases, however, the muscular elements may be discovered by the microscope lying amongst the fat, even though, to the naked eye, the muscle appear to be entirely converted into fat. Ultimately, the muscular fibres may undergo fatty degeneration and atrophy to complete disappearance.

This condition is frequent in animals which have been fattened—the fat not only increasing in the usual situations, but also accumulating between the fasciculi of the muscles; also in muscles which from any cause have for some time been incapacitated, and in which, consequently, circulation and oxidation are reduced to a minimum —*e. g.* in the extensors of the wrist-joint in cases of lead-poisoning, and in long-standing paralysis from lesions of the brain or cord; also in muscles which have been rendered useless by ankylosis of a joint. In progressive muscular atrophy, as Virchow has shown, the affected muscles exhibit this change, together with true fatty metamorphosis.

Fatty Infiltration of the Heart.—Obesity of the heart is not infrequent in general obesity and after pericarditis with adhesion, and must be carefully distinguished from the much more grave condition of fatty degeneration. In health there is a varying amount of fat beneath the visceral pericardium, always most abundant around the vessels in the grooves between the auricles and ventricles. This may increase so as to cover the right ventricle, but the left is rarely, if ever, completely enveloped; at the same time the fat may push in along the vessels between the muscular fibres, so that, on the right side, to the naked eye all appearance of muscular structure may be lost, the walls looking like a layer of fat, perhaps half an inch thick. In hearts less affected striæ of fat will be seen lying amongst the muscle. (See Fig. 7.) The fat is always most abundant near the surface, the muscular structure becoming more evident

toward the endocardium: at the base of the ventricles thick villous processes may form.

FIG. 7.

Fatty Infiltration of Heart: A section from the outer part of the left ventricle, showing growth of fat *between* the muscular fibres, in which in some places fatty metamorphosis is commencing. × 200.

The interstitial fat displaces and compresses the muscular fibres between which it lies, and diminishes the blood-supply and contractile power of the muscle, perhaps ultimately causing true fatty metamorphosis of the muscle (*q. v.*). These two processes not uncommonly go hand in hand, but it is difficult to speak dogmatically as to which in any given case is primary: fatty infiltration is probably possible only as the functional activity of the heart (or any other) muscle sinks, and the continued action of the causes leading to this depression would ultimately cause degeneration of the fibres; the presence of interstitial fat must, however, tend in the same direction. Fatty degeneration and atrophy of muscular fibres, on the other hand, is very likely to be followed by interstitial infiltration.

FATTY INFILTRATION OF THE LIVER.

CAUSES.—In the liver fatty infiltration is exceedingly frequent, constituting what is commonly known as the "fatty liver." This is

owing—first, to the excess of non-nitrogenous oxidizable matter in the portal blood; secondly, to the deoxidized condition of the portal blood; and, thirdly, to the low pressure and slowness of circulation in the portal vessels—conditions least favorable to oxidation,[1] most favorable to deposit of particles. The "fatty liver" is met with as part of general obesity and in conditions of diminished oxidation such as occur in phthisis.

PHYSIOLOGICAL INFILTRATION.—The hepatic cells always contain a small quantity of fat, which is temporarily increased after the ingestion of fatty substances. Ingestion of food rich in fat is followed by temporary excess of fat in the portal blood, and by the deposition and temporary accumulation of part of this in the hepatic cells. This fat is first deposited in the *circumferential cells* of the hepatic lobules, which are in immediate contact with the capillaries of the portal vein. From these it gradually passes to the central cells, whence it is ultimately conveyed again into the circulation. This process goes on until the excess of fat is removed from the blood and hepatic cells regain their former character. There is thus a transitory accumulation of fat within the hepatic cells, their vitality not being thereby impaired.

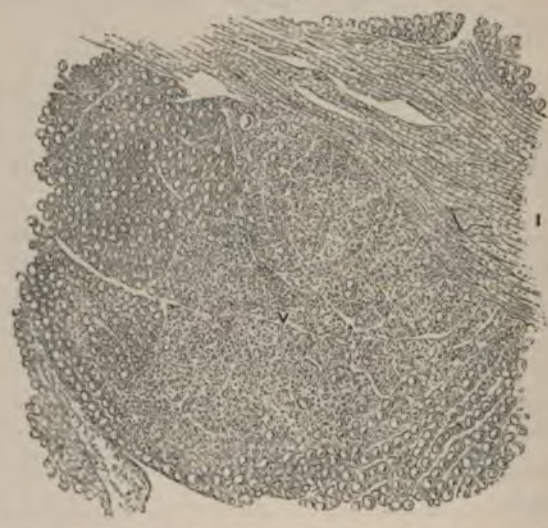
MICROSCOPIC CHANGES.—The morbidly fatty liver is one which constantly contains an abnormal quantity of fat, and here also, as the fat is usually deposited from the blood in the portal capillaries, the increase is first observable in the external zone of the hepatic lobules (Fig. 8). It accumulates here within the cells as minute globules which increase, coalesce, and form large drops of fat. These ultimately distend the cells, which become larger and more globular (Fig. 6). As the process advances the infiltration spreads from the periphery toward the centre of the lobule, until its whole mass may be involved and all its cells distended with fat. The vitality of the cells is not materially impaired by the infiltration, as is shown by the presence of bile in the stools and in the gall-bladder. In some exceptional cases the accumulation of fat is most marked around the hepatic vein. In these Virchow suggests that the fat is becoming excreted, and that only the last cells retain a little of it.

NAKED-EYE CHANGES.—The fatty liver is increased in

[1] *Lectures on Pathology and Therapeutics*, Bence Jones, p. 179.

size, in advanced stages to perhaps twice the normal. The surface is smooth, the edges are thickened and rounded, the specific gravity is diminished, although the absolute weight may be increased. If the infiltration be slight, involving merely the portal zone of the

FIG. 8.



Fatty Liver, showing accumulation of fat more especially in the cells of the external zone of the lobule. There is also some increase in the interlobular connective tissue (cirrhosis). V, hepatic vein; I, interlobular connective tissue. × 50.

lobules, the cut surface will present a mottled appearance, the external fatty zone being opaque, yellowish-white, whilst the centre is unaltered or is hyperæmic and appears as a red spot (fatty nutmeg-liver). The more extensive the infiltration, the larger is the pale zone, and ultimately, when the whole lobule is involved, there is left in the centre only a reddish-brown point—the commencement of the hepatic vein; in many cases even this point is lost. Then the organ is of an almost uniform opaque, yellowish-white color, and the boundary between the individual lobules may be completely obscured. In exceptional cases the accumulation of fat is much more abundant in some portions of the liver than in others, so that on section yellowish points and streaks are seen scattered over its surface. The consistence of the organ is much diminished, it feels doughy and pits on pressure with the finger, and the knife used to cut it becomes coated with oil. The pressure exercised by the infiltrated fat produces considerable anæmia of the organ, but the interference with

the circulation is *never sufficient to cause ascites, hemorrhage, or other evidences of portal congestion.*

CHAPTER IV.

FATTY DEGENERATION (Continued).

Fatty Metamorphosis.

This differs from fatty infiltration, inasmuch as the fat is formed by metamorphosis of the protoplasm of the cells themselves, and not from the fatty, saccharine, or nitrogenous principles of the food. There is reason to believe that cell-protoplasm, as it becomes effete, takes up oxygen and splits into a nitrogenous molecule (which is burnt to urea) and a non-nitrogenous molecule which forms fat. To repair its loss, the living protoplasm at the same time assimilates material it has prepared from the proteids of the food. In the process of healthy nutrition, destruction of small quantities of protoplasm and corresponding repair are constantly going on, and the products of the decomposition of effete albumen are immediately still further oxidized, rendered soluble, and removed. Consequently, we do not find in healthy cells fat-granules bearing witness to the occurrence of the above-described decomposition. When, however, a whole cell or many cells die and are protected from ferments, evidence of fatty matamorphosis of protoplasm is soon forthcoming. This we can watch in various physiological processes—*e. g.* the formation of milk, serum, cerumen, in all of which the fatty degeneration, death, casting off, and disintegration of superficial cells, and the constant production of new ones in the deeper layers, play a chief part. Evidence of the same decomposition of protoplasm is afforded by the transformation of entire bodies, which have lain for many weeks or months in water or damp soil, into *adipocere*—an ammonia or lime soap.

The origin from cell-albumen of the fat in fatty metamorphosis was first pointed out by Dr. Quain in his well-known researches on fatty degeneration of the heart.[1] He stated that the fat in the muscular fibres in this condition was the result of a metamorphosis of the

[1] *Medico-Chirurgical Trans. Lond.*, 1850, vol. xxxiii.

fibres themselves, and was not derived from without—a statement fully confirmed by the experiments of Voit and Bauer.[1]

These were made to determine the source of the fat in the acute fatty degeneration produced by poisoning with phosphorus. They gave phosphorus to dogs starved for some days previously, so that any fat in the tissues after death could not have been derived either from the food or from the adipose tissue of the animals. The phosphorus produced very extensive and general fatty degeneration, and the fat must obviously have arisen from the protoplasm of the cells. Voit concluded from these investigations—1st, that the transformation of cell-albumen is independent of the supply of oxygen, but that if oxygen be deficient the fat and other products of the transformation, being incompletely oxidized, accumulate in the cell; 2d, that the presence of fat in the cells may thus be due to increased transformation of the albumen or to diminished oxidation of the products of its decomposition; 3d, that the fatty degeneration in poisoning by phosphorus is due both to an increased transformation of the albumen of the cells, and to diminished oxidation of the fat and other products of the transformation.

CAUSES.—A study of various examples of fatty metamorphosis renders it clear that the occurrence of this change indicates the death of the protoplasm concerned, that the larger the proportion of the cell-albumen represented by fat the nearer is the whole cell to death, and that the nearer the cell is to death the more impaired will be its power of taking up oxygen and combining it with effete materials. Consequently, we may give the cause of fatty metamorphosis as **grave depression of the vital activity** of a cell, leading to—1, too rapid destruction of protoplasm, 2, lessened ability to repair losses; and 3, impaired oxidizing power. This depressed vitality is always the *proximate cause*, and is usually induced by (*a*) alteration in the quantity or quality of the food brought to the cell; (*b*) sometimes by altering the physical condition of the cell; but (*c*) the cell may be dying a natural death, so to speak, for there is a limit to the life of a cell as there is to the life of the body.

a. The effect of diminishing the blood-supply (*i. e.* food and oxygen) to a part is seen in the heart as the result of atheromatous changes in the coronary arteries, and in organs in which the lumen of the vessels

[1] Voit and Bauer: *Zeitschrift für Biologie*, vii. pp. 63-85; and Voit: *Neues Repertorium für Pharmacie*, xx. pp. 340-349.

is diminished by lardaceous or syphilitic changes. Working organs and tissues which have been long disused, and to which, consequently, the blood-supply is diminished, undergo fatty changes and atrophy until the blood-supply is sufficient to maintain them in equilibrium. Impaired circulation in a part—*e. g.* mechanical congestion—has a similar depressing effect. Fatty degeneration of the cells of cancers and other rapidly growing tumors and of inflammatory exudations is often due to insufficient blood-supply; but the cells may be naturally short-lived, and in inflammation the cause of the process must have an injurious action upon the leucocytes as well as upon the fixed cells. These variations in *quantity* of blood-supply act *locally*. Alterations in *quality* of the blood-supply act *generally*, and there are no cells which are not liable to undergo this change. Thus, fatty metamorphosis of the most important organs may result from chlorosis and the various forms of anæmia, from scurvy, from the addition to the blood of a protoplasm poison, like phosphorus. *b.* The action of prolonged high fever depends partly on the action of a high temperature on protoplasm, but the causes of the specific fevers and other circumstances probably cause blood-changes which act in the same direction. High external temperature tends to diminish oxidation. *c.* When the limit of life of a cell is approached, it undergoes fatty degeneration: thus we account for *senile* fatty metamorphosis of cells of cartilage, cornea, bone, and other parts.

MICROSCOPIC CHANGES.—The process consists in the transformation of the protoplasm of cells into molecular fat, which appears as minute granules, usually first in the protoplasm and subsequently in the nucleus. The granules—characterized by their small size, dark color, sharp contour, strong refractive power, blackening by perosmic acid, insolubility in acetic acid, and solubility in ether—gradually increase in number till the whole of the protoplasm may be transformed; some of them may coalesce and form distinct drops of fat. As the process advances the cells undergo an increase in size and become more globular in shape, the nucleus becomes involved, the cell-wall, when this exists, is destroyed, and the cell may thus be converted into a mass of fat-granules (Fig. 9).

Granule-cells may be of two kinds: dead or dying cells converted into masses of fat-granules, or living leucocytes (*granule-carriers*) which have taken up fat-granules, from a focus of degeneration, probably to convey them into the lymphatics and thus effect absorption.

Connective-tissue and neuroglia-cells near foci of degeneration similarly become charged with fat-granules. Granule-cells are often called "inflammatory" corpuscles or "corpuscles of Gluge." Typical granule-cells, formed by metamorphosis of epithelial cells or leucocytes, are the "colostrum"-corpuscles of the first milk secreted; later the degeneration is more complete, the cells break down, and their granules are suspended in the fluid, giving to it its opaque white color. The term "pathological milk" has been applied to the similarly formed fluid of many chronic abscesses.

FIG. 9.

Fatty Metamorphosis of Cells: *a*, from a cancer; *b*, from the brain in chronic softening. The latter show the large "granule-cells," and also the manner in which these become disintegrated. × 200.

Ultimately, fatty degeneration may affect connective-tissue fibres.

In old foci of fatty degeneration sheaf-like bundles of acicular crystals of margaric acid and rhombic crystals of cholesterin are found.

It is said that in fatty metamorphosis the percentage of fat in the tissue is but little increased; apparently many of the granules are formed by the invisible fat which is normally bound up with protoplasm as it were in an amalgam (Birch-Hirschfeld).

NAKED-EYE CHANGES AND DIAGNOSIS.—In advanced stages the change is recognized by slight or moderate swelling, which, however, is often replaced by more or less shrinking of the organ when absorption of the fat is going on, as in advanced acute atrophy of the liver; by the admixture of an opaque yellow with the normal tint of the tissue, giving a "faded-leaf" or brownish tinge to red organs, whilst in white or pale tissues the yellow itself is apparent—often in a patchy, spotty, or streaky manner, as the highest degrees of the change are usually reached only in limited areas; by loss of elasticity and by diminished consistence, the organ being flabby and its capsule wrinkling easily. Fat may be found upon the knife and evidence of structure (upon section) is obscured.

The microscope is necessary for the discovery of the earlier stages of this metamorphosis. This reveals the granular and somewhat swollen state of the cells; their larger size, higher refractive power, insolubility in acetic acid, solubility in ether, and blackening by perosmic

acid shows the granules to be fatty, and differentiates them from the albuminous granules of "cloudy swelling," soon to be described; lastly, the distinction must be made from fatty infiltration. Difficulty in this can arise only with regard to connective-tissue cells, liver-cells, and intestinal epithelium, in which infiltration or metamorphosis may occur; perhaps also the usual epithelium may contain infiltrated fat when this is being eliminated after severe contusions. The chief point of difference between the two processes is the size of the droplets, which are small in the metamorphosis, but run readily together in the infiltration. This holds good as a rule, but infiltrated fat exists in small droplets at first, and becomes finely divided before absorption, should this occur; on the other hand, largish drops may form in fatty metamorphosis, and are characteristic in the liver in acute atrophy and phosphorus-poisoning and in renal epithelium when the metamorphosis is at all advanced. Diagnosis may therefore occasionally be impossible. Evidence of destruction of cells is conclusive in favor of metamorphosis.

TERMINATIONS.—1. Absorption.—The fatty particles into which the cells have been transformed are, under favorable circumstances, readily absorbed. The degenerative process may cease and the fat be removed before the part has been dangerously involved. Such recovery probably often occurs, for example, in the kidneys and heart. Also when elements are completely degenerated the fatty débris is usually removed by absorption. This is seen in the fatty degeneration and absorption of inflammatory products, such as occurs in croupous pneumonia; in the degeneration and absorption of the cells of new growths, leading to central "cupping" or "umbilication" of nodules or to shrinking of the whole mass (atrophic scirrhus); and in the degeneration of small areas, such as results from embolism, thrombosis, or hemorrhage in the brain or other organ. As the result of such absorption we may have left a meshwork of vessels and connective tissue whence the essential cells have disappeared, as in the latter (red) stage of acute yellow atrophy; or we may have an ordinary scar, leucocytes having invaded the degenerate area and developed into fibrous tissue; or, lastly, a cyst of clear fluid may remain. For such absorption to occur the tissue round the degenerate cells must be freely supplied with blood.

2. **Caseation.**—In this mode of termination the fatty products are not absorbed, but gradually dry up into a yellowish friable material which has been compared to soft cheese. It results from disproportion between the degenerate mass and the vessels by which absorption

might be effected—a disproportion which is, in the first instance, the cause of the degeneration. It is most frequent in parts which contain but few vessels, or in which the vessels become obliterated by pressure from without or by thickening of their walls by endarteritis. Caseation is, consequently, most often met with in tubercular and gummatous masses and in rapidly-growing cancers and sarcomata.

Cheesy masses are constantly met with in lymphatic glands, brain, bones, and especially in the lungs, and considerable confusion has arisen as to their nature and origin. Formerly all cheesy masses were regarded as essentially tubercular; and it is true that tubercular lesions, being non-vascular, have a greater tendency than any others to caseate fully and to form typical cheesy collections. But, as just stated, other formations may undergo the same change; so caseation cannot be regarded as proving more than the occurrence of fatty degeneration. A caseous mass is tubercular only when it can be shown to contain the virus of tuberculosis; but it is doubtful if fatty degeneration of a gumma or of a rapidly-growing tumor ever gives rises to a typical "caseous" mass, such as we often find in lymphatic glands, the lungs, and elsewhere as the result of tubercular inflammation.

The process consists in a gradual drying up of the degenerate elements; the fluids are absorbed, the cells—which are many of them incompletely degenerated—shrivel and atrophy, the fat undergoes partial saponification, cholesterin forms, and the tissue thus becomes converted into a soft, yellowish-white, cheesy substance composed of atrophied cells, fatty débris, and cholesterin crystals. This material may gradually dry up more and more, and ultimately become encapsuled by a layer of fibrous tissue.

The caseous mass may subsequently become calcified or undergo a process of softening and liquefaction.

3. **Calcification.**—This is an advanced stage of the preceding process. It most frequently occurs when the caseous mass is completely shut off from the external air, as when in the lymphatic glands, in bone, or encapsuled in the lungs. The mass becomes infiltrated with calcareous particles, and is thus converted into a calcareous concretion. Single cells in a fatty focus may undergo this infiltration—*e. g.* ganglion-cells in an area of cerebral softening.

4. **Softening.**—An inflammatory cell-exudation, usually of tubercular origin, may undergo fatty metamorphosis, and, as its cells break up into granules, sufficient fluid is often effused to form a thin puriform liquid, usually containing curd-like cheesy masses: this looks

like pus, but consists of granules, fat-drops, and perhaps cholesterin crystals suspended in fluid ("pathological milk"). This is the pathology of **chronic abscess** of tubercular origin. If not discharged the fluid may be absorbed, leaving a caseous mass which may calcify.

Sometimes, after long quiescence, caseous and even calcified masses appear to excite sufficient irritation to result in the formation of an abscess and the discharge of the mass. The nature of the fresh irritant is unknown.

RESULT.—The effect of fatty metamorphosis is to impair or annihilate function. Recovery is possible only from early stages.

Fatty Degeneration of Blood-vessels.

ETIOLOGY.—Primary fatty degeneration of blood-vessels is in most cases a senile change; it is an expression of that general impairment of vitality which exists in advanced life, and is usually associated with similar changes in other parts. When, however, it is limited to the lining membrane of the largest arteries, it is often met with in early life and in persons who are otherwise perfectly healthy.

Fatty Degeneration of Arteries.—This may be **primary** or **secondary** to atheroma or other inflammatory condition of the vessels, the fatty change being preceded by cell-infiltration of the subendothelial connective tissue. (See "Atheroma.")

Primary fatty degeneration is not preceded by any disease of the parts affected by it. It may affect both the internal, middle, and external coats of the artery, but is most common in the first. The change usually commences in the endothelium and the subendothelial connective-tissue cells, small groups of cells becoming affected in various parts of the vessel; and it may gradually extend from within outward, the intercellular substance softening until, in exceptional cases, the whole thickness of the intima is destroyed (Fig. 10).

In the earlier stages this condition is recognized by the existence of small, irregular, opaque yellowish-white patches, projecting very slightly above the surface of the intima. These, which are so constantly met with on the lining membrane of the aorta, may at first be mistaken for atheroma. They are in most cases, however, readily distinguishable by their superficiality, and by the facility with which they can be stripped off from the subjacent layers, which present a

natural appearance. In atheroma, on the other hand—which affects the deeper structures—if the superficial layer be removed the opacity and thickening are seen to exist beneath it. In many cases the change is limited entirely to the innermost layers of the vessel; the more the subjacent tissues are involved, the greater is the irregularity in the shape of the patches and the less readily can they be separated with the forceps. The opaque patches occasionally break down, the cells are destroyed, the intercellular substance softens, and the granular débris is carried away by the circulation, leaving small, irregular, superficial erosions upon the lining membrane of the vessel. These erosions are not ulcers in the true sense of that term, not being the result of an active process. They resemble the superficial erosions so common upon the mucous membrane of the stomach, as described by Dr. Wilson Fox.

Fig. 10.

Fatty Degeneration of the Internal Coat of the Aorta: small yellowish-white patches scattered over the lining membrane of the vessel. A very thin layer peeled off and × 200, showing the groups of fat-molecules and the distribution of fat in the intima.

Simple fatty degeneration may occur in any artery, but it is in the smaller ones, in which it is more especially liable to affect the external coat (Fig. 11), that its injurious influence is most marked. Here, by diminishing the elasticity and contractility of the vessels, it causes degenerative changes in the parts which they supply, and often leads to rupture. This is exemplified by many cases of chronic cerebral softening and cerebral hemorrhage, although here atheromatous are often associated with the simple fatty changes. In the larger arteries, as the aorta—where it is exceedingly common—it is of less importance, the inflammatory process, atheroma, having here a far more deleterious effect.

Fig. 11.

Fatty Degeneration of Small Vessels of Pia Mater, from a case of chronic Bright's disease: *a*, a small artery, the coats of which are somewhat thickened; *b*, a capillary, in which are seen a few red blood-corpuscles. × 400.

Fatty Degeneration of Capillaries.—The capillaries may also be

the seat of fatty changes, especially in the nervous centres, and in the kidneys in Bright's disease. (See Fig. 11, *b*.) The process commences in the endothelial cells, and may involve considerable areas of the capillary wall, so that rupture is often the ultimate result. This is common in the smallest cerebral blood-vessels, where it is sometimes a cause of cerebral (capillary) hemorrhage.

Fatty Degeneration of Muscle.

Both striated and non-striated muscle may be the seat of fatty degeneration. In both the muscular fibre-cells are the seat of the change; they become filled with fat-granules and are ultimately destroyed: the process thus differs essentially from **fatty infiltration** (p. 55).

In **non-striated muscle** this change is frequently met with in the middle coat of arteries which are undergoing fatty degeneration.

In **striated muscle**—both in the voluntary and in the involuntary of the heart—the earliest stage of the affection is characterized by an indistinctness in the transverse markings of the fibres, which in many parts become studded with minute particles of fat (Fig. 12). These gradually increase in number and size, but almost always remain small, and are usually distributed somewhat irregularly within the sarcolemma. In some parts single rows of granules are found running along the length of the fibre; in others they are grouped around the nuclei or arranged in transverse lines corresponding with the striæ of the muscle. The fibres become extremely friable, and are readily broken up into short fragments. As the process advances the transverse markings entirely disappear, and nothing but molecular fat and oil-globules are seen within the sarcolemma. The sarcolemma itself may ultimately be destroyed, and nothing remain of the original fibre but the fatty débris into which its albuminous constituents have been converted. This is true "fatty degeneration" of muscle.

Fig. 12.

Fatty Degeneration of Muscular Fibres of Heart: *a*, earlier stage; *b*, more advanced. × 400.

Fatty Degeneration of the Heart.

It is in the heart that fatty degeneration of muscle is most frequently met with, and here it assumes a most important aspect from the deleterious influence which it exercises upon the motor power of

the organ. The degeneration may be diffuse or circumscribed, acute or chronic. The wider the extent of tissue that is affected, the less advanced, as a rule, is the degree of degeneration. It is in those cases in which small tracts of tissue only are involved that the process is met with in its most advanced stage.

When the change is slight and more or less general, the muscle is somewhat softer and more flabby than natural; it is more friable, and often breaks with a soft granular fracture, and its color is rather paler and more opaque than that of healthy cardiac tissue. The microscope shows the muscular fibres to have lost to some extent their striation and to contain granules of fat (Fig. 13, *a*).

The diffuse form of degeneration may be due to—1. Diseases in which the oxidation processes are reduced to a minimum in cases which are attended by marked anæmia, whether gradually or rapidly

FIG. 13.

Acute Fatty Degeneration of Heart and of other Muscles: *a*, heart; *b*, rectus abdominis. The whole of the heart-tissue was affected, and also the muscles in other parts of the body. × 400.

induced: such are anæmia from repeated or excessive bleeding, pernicious anæmia, advanced leukæmia, malignant and other cachexiæ. The accompanying drawing (Fig. 13) was taken from the case of a weakly young girl who was under my care suffering from slight valvular disease. She quickly succumbed with acute fatty degeneration of the heart and other muscles, induced by a profuse loss of blood

during a menstrual period and by inability to retain food.[1] 2. Certain poisons, especially phosphorus, but also arsenic and the mineral acids, in cases surviving a few days. 3. Acute infective febrile diseases, especially diphtheria, in which a somewhat high degree of degeneration may be attained and be the cause of sudden death. Interference with the circulation in the coronary arteries is also a frequent cause of a more or less general degeneration of the muscular tissue. This occurs especially as a result of aortic incompetence, and explains the early failure of cardiac power in this form of valvular disease. Atheromatous changes at the orifices of these arteries lead in the same way to diffuse fatty degeneration. Adhesive pericarditis and myocarditis act similarly; they also hamper the heart mechanically, and the cause of the inflammation acts injuriously on the muscle-cells.

Sometimes the degeneration, although perhaps more or less general, is much more advanced in some parts than in others. In such cases the heart presents a mottled appearance: opaque pale-yellowish or brownish patches are seen irregularly distributed throughout its substance. These patches, which vary considerably in size and form, are met with especially in the papillary muscles, the columnæ carneæ, and in the layers of fibres immediately beneath the endocardium. They may also occur beneath the pericardium and in the deeper portions of the organ. They correspond with the most degenerated portions of the tissue. They are soft and flabby, and have a rotten consistence, tearing readily under the finger. Under the microscope the fibres are seen to be in an advanced stage of fatty degeneration, their sarcolemmata containing molecules of fat- and oil-globules, which in many parts have escaped and lie free amongst the surrounding less degenerate tissues (Fig. 12, *b*). These more localized degenerations are most common in old people, and usually result from considerable disease of some branches of the coronary blood-vessels, and not from conditions of general anæmia. The peripheral layers of muscular tissue also frequently undergo extensive fatty degeneration as the result of pericarditis. The connection between these localized degenerations and rupture and aneurism of the heart is well known.

BROWN ATROPHY OF THE HEART.—Somewhat allied to, and occasionally associated with, fatty degeneration of the heart is the condition known as brown atrophy. This consists in a gradual atrophy of the muscular fibres, together with the formation of granules of brown-

[1] *Trans. Clin. Soc. Lond.*, vol. viii., 1875.

ish-yellow or blackish pigment. These granules of pigment, which are probably the coloring matter of the muscle, are either grouped in clusters around the nuclei or more generally distributed within the fibre. The fibres are frequently, at the same time, the seat of more or less fatty degeneration (Fig. 14). This change usually occurs as a senile one or as a part of general marasmus from other causes. It is also met with in some cases of cardiac hypertrophy. Its recognition is in most cases impossible without the aid of the microscope.

FIG. 14.

Brown Atrophy of the Heart: showing the granules of pigment and the atrophy of the fibres. The latter have in some parts undergone slight fatty metamorphosis, × 400.

FATTY DEGENERATION OF THE KIDNEYS.

Fatty degeneration of the kidneys frequently occurs as a result of inflammation of the organs. This **secondary** degeneration will be alluded to when treating of renal inflammations. **Primary** fatty degeneration is much less frequent. It must be borne in mind that the renal epithelium very commonly contains more or less fat, but it is only when this is excessive that it can be regarded as a diseased condition. This excessive formation of fat in the kidney is, I think, less common than is generally supposed. It is, however, occasionally met with in chronic diseases, especially in pulmonary phthisis. It is also a result of poisoning by phosphorus.

In simple fatty degeneration the change is usually confined to the epithelium of the cortex. The cortex presents on section a somewhat yellowish-white surface, often slightly mottled; and this, in most cases, is most marked near the bases of the pyramids. There is no adhesion of the capsule or granulation of the surface. Microscopically, only the nuclei of the vessels and of the connective tissue stain well. This change appears to interfere but little, if any, with the functions of the organs, and in this respect it resembles the analogous change in the liver. It is not usually accompanied by albuminuria.

CEREBRAL SOFTENING.

This is perhaps the most suitable place to speak of cerebral softening, inasmuch as fatty degeneration of the brain-tissue usually constitutes a prominent feature in the historical changes. Softening of the cerebral substance is essentially a necrotic process, and may result

from any condition interfering with blood-supply—viz. inflammation, embolism, thrombosis of arteries or (much more rarely) of veins. Portions of the brain which are the seat of this change may be merely rather softer than the surrounding healthy tissue, breaking down more readily under a stream of water which is allowed to fall upon them, or they may be completely diffluent. They are never distinctly circumscribed, but pass by insensible gradations into the neighboring tissue.

Under the microscope the change is seen to consist in a disintegration of the nerve-tissue. The fibres suffer earliest: their white substance first coagulates, then breaks up into masses of various sizes (myelin), which give place to masses of fine fat-granules; these probably consist chiefly of fat liberated from the sheath of Schwann rather than formed by metamorphosis of albumen.

Next, when gray matter is implicated the large nerve-cells are involved in the necrotic stage, but though full of granules their outline may long remain visible. Lastly, the neuroglia-cells and those of the small blood-vessels degenerate similarly, and the tissue is thus converted into broken-down fibres, granular matter, and molecular fat, amongst which are many granule-cells (p. 66). These corpuscles are most common and form characteristic objects in cerebral softening (Fig. 15): they vary from $\frac{1}{500}$ to $\frac{1}{2000}$ inch in diameter, and the granules they contain are probably often myelin and not fat. Many are formed by degeneration of ganglion-cells and neuroglia-cells, but many—perhaps most—are leucocytes which have taken up granules. Ultimately, all trace of structure is lost.

The color of the softened portion varies considerably, chiefly with the amount of blood in the vessels or extravasated into the tissues. It may resemble that of the surrounding healthy tissue or be of a yellowish or reddish tint. According to these variations in color cerebral softenings have been classified into **white, yellow,** and **red.** As, however, a yellow softening may be but a later stage of red, as white may be succeeded by red due to hemorrhage into the area, and as softenings of inflammatory and of simple degenerative origin may be to the naked eye indistinguishable, this classification has little practical or scientific value.

WHITE SOFTENING is sometimes **acute,** being due to embolism of one of the larger arteries, usually soon causing death; but far commonly it is **chronic,** occurs especially in the aged, and is due to gradual narrowing of the arteries by chronic endarteritis (atheroma), senile

impairment of the heart-force being a subsidiary cause of imperfect blood-supply. Narrowing of the arteries from syphilitic endarteritis will act similarly and earlier in life. The process is really one of simple necrosis, sudden or gradual: in the latter case there is no reason for hemorrhage, and as to the former it is a fact not certainly explained that infarction is rare after embolism of the brain. Consequently, the softening area is untinged by blood, and presents either a dirty-white color or looks like the brain around. It may be merely softened or diffluent, and may result in a cyst of clear fluid *without any blood-pigment in its wall* or in a scar—the latter appearing at first as a meshwork the spaces of which are full of milky fluid. Before the circulation has ceased and the death of all the elements in an area of white softening is complete a fattily-degenerated vessel may burst into the area and transform it into one of red softening.

FIG. 15.

Chronic White Softening of the Brain: granular corpuscles, broken-down nerve-fibres, and fat-granules, of which the softened substance is composed. The one or two nucleated cells are probably nerve-cells. × 250.

RED SOFTENING.—This is commonly dependent upon vascular obstruction, either from embolism or thrombosis. There is collateral hyperæmia, rupture of capillaries, and extravasation of blood; the softened tissue usually exhibits red points and patches mingled with white and yellow; the patch is swollen in proportion to the hemorrhage and œdema, and is rarely diffluent. Red softening is most common in the vascular gray matter of the cortex and of the basal ganglia. Red softening is also sometimes associated with the chronic white variety (see above). Lastly, it may be inflammatory. (See "Inflammation of the Brain.")

YELLOW SOFTENING.—This is a later stage of red softening, and like it is usually situate in gray matter—chiefly of the convolutions. The color is due to the presence of altered blood-pigment, the result of the previous extravasation. The pigment may be seen as fine dark granules and hæmatoidin crystals, scattered through the cells of the neurolgia and the nerve-cells of the gray matter; at first sight the granules look like fatty particles, but are distinguished by their dark, black color. White and yellow softening may remain unchanged for long periods.

CHAPTER V.

CLOUDY SWELLING (PARENCHYMATOUS OR GRANULAR DEGENERATION, ALBUMINOUS INFILTRATION).

THIS is a very frequent change, being found in all diseases attended by considerable pyrexia. Wickham Legg and Liebermeister, having produced it by submitting animals to a high external temperature, regard the change as due simply to the fever, which, they say, causes increased destruction of albumen. This, however, seems like arguing in a circle, for it is increased destruction of tissue which produces the elevation of temperature: moreover, the change is not most marked in long-continued secondary fevers, but in the relatively short primary fevers of the acute specific diseases. Further, the degeneration is specially pronounced in bad cases of diphtheria, in which disease the temperature is often low. All this leads to the belief that the infective material in the blood—the cause of the fever—has a more or less deleterious action on the tissues. This is supported by the observation that cloudy swelling is the first change noticeable in poisoning by phosphorus, arsenic, and the mineral acids, all of which lead ultimately to fatty degeneration of protoplasm. Lastly, cloudy swelling is found in inflamed parts, and we shall see, when considering inflammation, that it is always due to the action of an irritant which, if it were of sufficient intensity, would produce death of the tissue. It would appear, therefore, that cloudy swelling is due to the action upon the tissues of some noxa which *tends* to cause their death: elevation of the temperature of protoplasm above the normal undoubtedly acts in this way.

In considering the histology of this change we shall find that advanced cloudy swelling passes insensibly into fatty metamorphosis: it is, therefore, to be regarded as *the first step toward fatty metamorphosis.*

SEATS.—The large masses of protoplasm naturally show the change most plainly—the liver, kidneys, and muscles—but probably all protoplasm suffers. The change may be much more advanced in

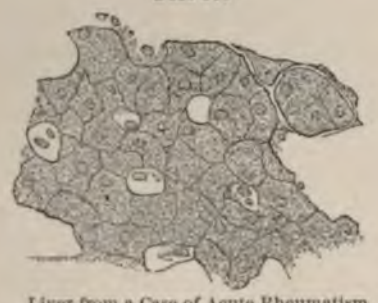
some organs than in others, owing perhaps to differences in the local circulation.

NAKED-EYE APPEARANCES.—When the change is well marked the organs (liver or kidney) are slightly swollen, and may be either anæmic or slightly hyperæmic; the surface of a section bulges up somewhat, the tissue is more or less markedly opaque, and is softer than natural.

MICROSCOPIC APPEARANCES.—The cells are swollen and their protoplasm is finely granular, the nucleus and any cell-structure being obscured or even indistinguishable: the granules refract light but feebly; they dissolve in dilute acetic acid, but not in ether, and are therefore albuminous. In advanced cases, larger, strongly-refracting granules, blackening with osmic acid, soluble in ether, but not in acetic acid (fatty), are found associated with the albuminous granules which would first appear like a precipitate in the cells.

EFFECTS.—Doubtless this change impairs, in proportion to its degree, the vital activity of the cell: yet there can be no doubt but

FIG. 16.



Liver from a Case of Acute Rheumatism with High Temperature: the liver-cells swollen and granular, the nucleus in many being almost indistinguishable. × 200.

FIG. 17.

Muscular Tissue of the Heart, from a Case of Severe Typhoid Fever: the fibres are granular, the nuclei obscured, and the striation lost. × 400.

that it is completely recovered from and disappears, leaving no trace, when the disease producing it does not prove fatal. Of course its most serious action is upon the heart.

The Liver.—Here the change is usually most marked, and is absolutely typical (Fig. 16).

The Kidneys.—The cortex is typically affected. The Malpighian

bodies and the pyramids are usually hyperæmic, and contrast with the pale cortex. The tubal epithelium presents the appearances above described; they are well seen in the early stages of tubal nephritis.

The Heart and Muscles.—The heart becomes slightly opaque, pale, and soft. The muscular fibres are finely granular, and have lost their distinct striation (Fig. 17). Such a condition must materially interfere with the contractile power of the organ. A similar change is met with less frequently in other muscles.

The Lungs.—The change cannot be recognized by the naked eye. The epithelial cells, according to Buhl,[1] swell and become markedly granular from the presence of albuminous and fatty particles, and they become loosened from the alveolar walls.

CHAPTER VI.

MUCOID AND COLLOID DEGENERATION.

Mucoid Degeneration.

DEFINITION.—Mucoid degeneration consists in the transformation of the albuminoid constituents of the tissues into **mucin.**

Chemically, mucin is closely allied to albumen, more so than to either gelatin or chondrin. Like albumen, it is met with only in alkaline fluids, being held in solution by the free alkali; it is precipitated by dilute acetic acid and alcohol. It differs from albumen in not containing sulphur, in being insoluble in an excess of the acid, and also in not being precipitated by boiling, by tannin, or by bichloride of mercury. These two reagents will distinguish it also from gelatin and chondrin, which are both precipitated by them.

CAUSE.—This is unknown. It appears to be a reversion to an earlier state, for in the fœtus the connective tissues consist almost entirely of soft mucin-yielding substance; the umbilical cord and vitreous humor retain this peculiarity. Throughout life a mucoid change occurs physiologically in the secretion of mucus; a clear drop of mucus appears in the protoplasm, and increases till the cell

[1] *Lungementzundüng, Tuberkulose, und Schwindsucht.*

bursts and the mucus is evacuated—the cell not being destroyed, as a rule.

In **myxœdema** all connective tissue is more or less infiltrated with a fluid containing a large quantity of mucin. The disease affects adults, generally females, and appears to be due to atrophy of the thyroid body.

SEATS.—*Pathologically*, mucoid degeneration may affect both cells and intercellular substance. It is met with in catarrh of mucous membranes, the transformation occurring much more rapidly than under normal conditions, and the cells being often cast off; also in connective tissue, cartilage (especially the intervertebral and costal cartilages of old people), in bone, and in many new growths, not only in those of connective-tissue type, but in both cells and matrix of cancers.

NAKED-EYE APPEARANCES.—The affected parts are transformed into a homogeneous colorless material of a soft, mucilaginous, jelly-like consistence. If the change is limited to isolated portions of the tissue, the softened parts surrounded by those which are unaltered often present the appearance of cysts. These cyst-like formations containing mucoid substance are not uncommonly met with in the costal cartilages and in new growths.

MICROSCOPICAL CHANGES.—These are the same as in the physiological process, but the cells are much more frequently destroyed.

EFFECTS.—Complete mucoid degeneration implies abolition of function.

Colloid Degeneration.

DEFINITION.—Colloid degeneration consists in the metamorphosis of cell-protoplasm into a substance known as "**colloid.**"

Chemically, colloid differs from mucin in containing sulphur and in not being precipitated by acetic acid or alcohol.

In the adult many vesicles of the thyroid contain colloid; it is only when the formation of this material becomes general and excessive, producing one form of goitre, that the process is here to be regarded as pathological.

CAUSE.—This is quite unknown.

SEATS.—Colloid degeneration occurs most often in the thyroid; then in certain new growths, both sarcomata and cancers, and the secondary growths in glands and elsewhere will undergo the same change. It must be remembered that the term "colloid tumor" implies nothing as regards the nature of the growth. Other seats are rare.

NAKED-EYE APPEARANCES.—Colloid is colorless or pale yellow, glistening, and has the consistence of rather soft gelatin, which, indeed, it much resembles. Quite small points of colloid catch the eye; they do not stain characteristically with iodine or the aniline dyes. The physical characters of colloid tissues are thus very different from those of mucoid tissues. In advanced stages, however, colloid may soften, and masses of softened colloid, separated by septa of comparatively undegenerate tissue, give the appearance of cysts in a tumor.

MICROSCOPICAL CHANGES (Fig. 18).—One or two small masses of colloid appear in the cell, increase, and push aside the nucleus until they have replaced all protoplasm and the cell is considerably swollen. The nucleus usually atrophies and disappears, but may become colloid. Neighboring cells coalesce into small masses, and these again into larger, which not uncommonly, under the microscope, look as if they were concentrically laminated. Thus the cavities full of colloid, above mentioned, are formed. Intercellular substance atrophies rather than degenerates, whilst in mucous degeneration the matrix is frequently affected by the morbid process.

FIG. 18.

Colloid Cells, from a colloid cancer (Rindfleisch).

EFFECTS.—Abolition of function proportionate to the extent of the metamorphosis.

ZENKER'S DEGENERATION OF MUSCLE.

This change has been regarded as allied to colloid degeneration, but its nature is doubtful. It was first described by Zenker as occurring in the muscles in typhoid, and chiefly in the recti abdominis

adductors of the thigh, the diaphragm, and tongue muscles. It is now known to occur, though less often, in other infective febrile diseases (smallpox, cerebro-spinal meningitis, trichonosis); also in the neighborhood of burns, bruises—either before or after systemic death—abscesses and tumors of muscle. Probably, as Cohnheim suggested, the unusual appearance of muscle thus affected is due to a disturbance in the ordinary post-mortem coagulation of myosin; *i. e.* "Zenker's degeneration" is an example of coagulative necrosis. The appearance may certainly be produced after systemic death, and almost certainly occurs during life in fibres dying from any cause.

NAKED-EYE APPEARANCES.—The portions of muscle affected are semi-opaque, pale, slightly lustrous, of a reddish-gray or brownish-yellow color, and abnormally friable. They appear somewhat like the muscle of frogs or fish. The fibres are never universally affected, but many normal are associated with altered elements.

Fig. 19.

A Portion of the Soleus Muscle from a Case of Typhoid Fever: preparation teased after treatment with Müller's fluid. × 200, reduced ⅓.

MICROSCOPIC CHANGES.—The altered fibres are much swollen, the transverse striation lost, and the sarcolemmata occupied by a homogeneous structureless material, which is exceedingly brittle, and usually presents a wrinkled appearance or is broken up transversely into several irregular fragments (Fig. 19).

EFFECTS.—This change necessarily impairs the contractile power of the muscle, and it is believed often to lead to rupture of some of the fasciculi and hemorrhage. The dead fibres appear to be readily absorbed and quickly regenerated.

Hyaline Degeneration.

This name was given by v. Recklinghausen to a morbid change characterized by the appearance in cells of drops of a substance having an appearance like that peculiar to albuminoid degeneration, but

not giving the color-reactions of the latter. It is stained pale yellow by iodine, and in other respects seems allied to "colloid." It is said by v. Recklinghausen to be a normal constituent of cell-protoplasm, and to be set free when the cell dies. Very little is known about the substance, however, and there is a tendency on the part of some writers to include under this heading all morbid changes resulting in a hyaline appearance, and especially those due to coagulative necrosis.

The chief seats of this change appear to be the arteries of the brain and of lymphatic glands; in arterioles the adventitia is converted into a shining thickened layer. In larger arteries becoming aneurismal, Meyer has described the yielding as being due to hyaline degeneration starting internally and passing outward. The same degeneration is said to be frequent in inflamed parts, the connective tissue being affected. Gull and Sutton have described a hyalin-fibroid change in the arteries in chronic Bright's disease.

CHAPTER VII.

LARDACEOUS (WAXY OR AMYLOID) DEGENERATION.

THIS, which is one of the most important degenerative processes, is characterized by the appearance in the tissues of a colorless, translucent, firm, lardaceous substance, giving them somewhat the appearance of boiled bacon or of white wax, resisting gastric digestion and staining characteristically with certain reagents. The reaction with iodine led Virchow, its discoverer, to regard the substance as allied to starch and to propose for it the name "amyloid substance."

Chemical Nature of the New Material.—By submitting degenerate organs to gastric digestion the substance may be obtained practically pure; and, thus obtained, it has been shown by Kühne to be nitrogenous, closely allied to albumen, and not starchy. It is distinguished from albumen chiefly by its resistance to the action of dilute acids and alkalies, of the gastric juice at the body-temperature, and of putrefaction; also by certain color-reactions.

Dickinson regards the substance as fibrin deprived of its alkaline salts, which he supposes are carried away in the pus; but this would not account for all cases of lardaceous degeneration.

Marcet has shown[1] that the affected organs are notably deficient in potash and phosphoric acid, but they contain excess of soda and chlorine.

With regard to its **color-reactions** the best and longest known is that with iodine. To obtain this, wash a surface of section thoroughly to free it from blood, and then pour over it a watery solution of iodine (.5 per cent.) and iodide of potassium (1.5 per cent.); lardaceous portions are quickly stained dark mahogany-brown, the healthy tissues assuming a bright-yellow color: degenerate glomeruli, with their afferent arteries, may thus be readily recognized, and still greater delicacy may be obtained by floating well-washed, thin sections, made with Valentin's knife, for some minutes in the iodine solution. If this stained surface be treated with a 10 per cent. solution of sulphuric acid, degenerate parts assume, either at once or after some time, a dark greenish, bluish, or blackish hue, whilst healthy parts become grayish; this reaction is very variable and of little value.

For microscopic purposes it is said that this reaction may be obtained by staining the sections with iodine, mounting them in glycerin and placing at the edge of the cover-glass a very small quantity of strong sulphuric acid; in about twenty-four hours, usually, the lardaceous tissues are stained blue. But a more valuable, though still somewhat variable, process is that of staining the sections with aniline violet (10 per cent. in water or glycerin); after some hours, generally, the degenerate parts are stained bright magenta, the healthy blue (Jürgens, Cornil). This staining is more permanent than that by iodine, and is valuable as a confirmatory test; for the iodine reaction may be obtained with other forms of altered albumen, and cannot be regarded as absolutely characteristic of lardaceous degeneration.

ETIOLOGY.—Lardaceous degeneration is said to be much commoner in males than in females, and the ages of the great majority of patients fall between ten and thirty, especially between twenty and thirty. It is almost always *secondary* to prolonged and profuse suppuration, due usually to tubercular disease of lung, bone, joint, or kidney, but sometimes to traumatic (septic compound fractures) or other causes (dysentery, actinomycosis). Much less commonly it is found in the cachexia of tertiary syphilis, especially when there is chronic bone-disease. Rarely it appears in the cachexia of severe malaria, of leukæmia, and of cancer, and very rarely, especially in

[1] *Trans. Path. Soc. Lond.*, 1871, rep. on "Lardaceous Disease."

children, the degeneration may seem to be *primary*. Most of these diseases belong to the class of infective diseases, and Birch-Hirschfeld suggests that the degeneration may be due to an infective cause, but he adduces no evidence in favor of this.

The degeneration may be very rapid (two to three months, Cohnheim) in appearing, or, under apparently similar circumstances, its onset may be long delayed; this is more likely to be the case in young children than in adults. Like hectic fever, this degeneration occurs much more readily from suppuration of foul, ill-drained cavities than from a much more free discharge from a cutaneous ulcer, upon which the pus cannot accumulate under pressure.

SEATS.—The change is almost always widely distributed: rarely it is limited to one organ. It may affect almost all organs and tissues, and occurs most commonly in the **spleen**, then in the **liver, kidneys,** and **intestines,** and **lymphatic glands**; less frequently, and when the change in these is advanced, minor degrees of it may be found in the stomach, suprarenal capsules, pharynx, œsophagus, bladder, prostate, and generative organs, serous membranes, the membranes of the brain and cord, and muscle. There is no rule as to the order in which the organs are affected or as to which will be affected in any given case. As a **local change,** apparently quite distinct from the condition indicated by "lardaceous degeneration," it occasionally affects **pathological** products, as old thrombi, inflamed glands, scars (especially syphilitic), and tumors.

NAKED-EYE APPEARANCE.—Organs (*e. g.* spleen, when diffusely affected and liver) in which this change is at all advanced present features so characteristic that its nature can be readily recognized by the naked eye. They are usually considerably increased in size, but their general form is preserved, any edges becoming more or less rounded; their absolute weight is increased, and also their specific gravity; their surface is smooth, and the capsule tense and stretched; their consistence is firm and somewhat elastic. On section they exhibit a peculiar homogeneous, glistening, translucent appearance, somewhat resembling pure white wax. Owing to the diminished calibre of their blood-vessels and to the pressure exercised by the new material they contain but little blood, and hence are always pale in color. In slighter degrees of the change spots and patches of the morbid material may be scattered like grains of boiled sago through

the tissue (**sago spleen**). The color reactions above mentioned should always be used, and will reveal altered patches—*e. g.* in intestine—not yet obvious to the naked eye; but for the recognition of the degeneration in its earliest stage the microscope is necessary. *The presence of lardaceous degeneration is often marked by some other change, especially fatty.*

MICROSCOPIC CHANGES.—The morbid substance usually appears first in the subendothelial connective tissue of the **arterioles** and **capillaries**, and in the media of the former; the endothelium is unaffected and the adventitia usually escapes. The change greatly diminishes the lumen of the vessel; it does not affect the latter uniformly, but frequently causes spindle-shaped enlargements; and not only do the vessels of many parts escape entirely, but the distribution of the change in an affected organ may be quite irregular.

With regard to the further spread of the change, all authorities of recent date appear agreed that the connective tissue in every organ suffers chiefly and swells into homogeneous waxy-looking masses, frequently coalescing, between which the essential cells of the organ atrophy even to disappearance. With perosmic acid and ordinary staining reagents Ziegler says that there is no difficulty in demonstrating the liver-cells between the homogeneous blocks into which the connective tissue has swollen (Fig. 20, from Rindfleisch, and said by him to represent degenerate liver-cells). Many writers deny that epithelial cells can undergo the change; others, like Ziegler, content themselves with saying that they may be quite unaffected in advanced stages of the disease. Opinions differ as to whether muscle-cells and those of lymphatic glands become lardaceous.

FIG. 20.

Lardaceous Liver-Cells (see text): *a*, single cells; *b*, cells which have coalesced. × 300 (Rindfleisch).

The primary change may occur in the connective tissue of an organ, and not in the vessels.

EFFECTS.—The result of diminishing the blood-supply to the essential elements of a part by narrowing the arterioles and by direct pressure on the elements is naturally to cause atrophy, frequently accompanied by fatty degeneration (p. 48), and proportionate dimi-

nution of function follows. The change in the vessel-walls alters the quantity and quality of the transudation, as is shown by the changes in the urine when the kidneys are affected.

It seems probable that removal of the cause—*e. g.* chronic suppuration—of lardaceous degeneration may lead to arrest of the deposit, and perhaps to its removal from diseased organs, even in marked cases; but in the great majority of instances the change is steadily progressive, and proves fatal by exhaustion, led up to by anæmia, hydræmia, albuminuria, and diarrhœa—all of which are easily accounted for by the morbid anatomy. But the effect of the primary disease also must always be rememembered.

NATURE OF THE DEGENERATION.—Is the process an infiltration or a metamorphosis? It is generally regarded as an infiltration, a soluble lardaceous substance from the blood being deposited in tissues predisposed by some morbid change to receive it and combine with it into the very insoluble "lardaceous substance;" the latter change accounts for the irregular distribution of the degeneration. A parallel was drawn by Virchow between this degeneration and calcareous infiltration, in which the deposit of salts occurs only in dead tissues. The nature of the process is, however, by no means certain, some facts supporting the view that it is metamorphosis—*e. g.* the occurrence of the lardaceous substance in thrombi, and perhaps in casts. We have already alluded to Dr. Dickinson's view[1] that the substance deposited from the blood is de-alkalized fibrin, rendered insoluble by loss of alkali due to the drain of pus (see "Pus") from the system. But this explanation fails to cover many cases, and Budd considers that such a substance should digest easily.

Seegen is quoted by Kyber[2] as having found in normal blood a substance ("dystropodixtrin") having the peculiarities of the lardaceous substance; he believes that this substance loses its solubility and is deposited.

Lardaceous Degeneration of the Liver.

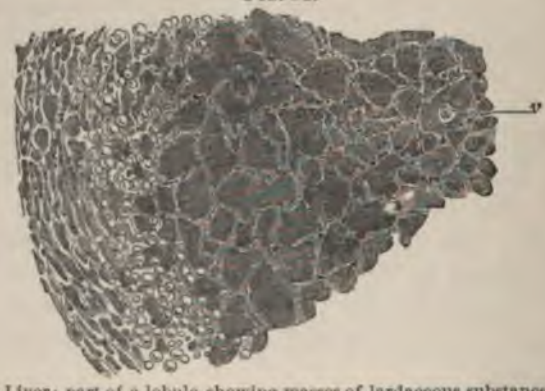
NAKED-EYE CHANGES.—The lardaceous liver is increased in size, perhaps even so much as almost completely to fill the abdominal cavity. Its weight is increased, and also its specific gravity. The enlargement being uniform, the natural shape of the organ is little

[1] *Med.-Chir. Trans.*, vol. i.
[2] *Virch. Arch.*, lxxxi. p. 278, and *Dissertation*, 1877.

altered; the edge is rounded, the surface smooth, and the capsule appears tense and stretched. The consistence is firm and elastic. The cut surface is dry, bloodless, smooth, translucent, and waxy-looking, and of a pale reddish-gray or dirty-yellow color. If the change is very far advanced, the tissue may be perfectly homogeneous, all distinction between the individual lobules being lost. In other cases the lobules are distinctly mapped out; they are enlarged, and the external zone may be of an opaque yellowish-white color, owing to the presence of fat. This association of the fatty and lardaceous changes is exceedingly common. Lardaceous degeneration does not obstruct the portal circulation, and hence does not cause ascites. It causes fatty degeneration and atrophy of the hepatic cells, and thus interferes with the functions of the organ.

If thin washed sections of a liver in an early stage of the affection be examined, the staining will be found limited to the so-called "intermediate zone" of the lobules, the area of distribution of the hepatic artery. The earliest seat of lardaceous degeneration thus differs from that of fatty infiltration, in which the fat first accumulates in the cells of the outer or portal zone (Fig. 21), and also from that

FIG. 21.



Lardaceous Liver: part of a lobule, showing masses of lardaceous substance, resembling in section degenerate and fused hepatic cells, and greater implication of the intermediate zone. Externally are seen several fatty cells, a certain amount of fatty infiltration being associated with the lardaceous change. *v*, hepatic vein. × 100.

of pigmentation of the hepatic cells from mechanical congestion, which begins in the central zone around the hepatic vein. All these changes not uncommonly occur together. As the lardaceous change advances, the whole lobule and interlobular connective tissue may become involved.

HISTOLOGY.—The change usually begins in the walls of the

capillaries and arterioles of the hepatic artery; rarely, it is said, in the capillaries of the portal vein. Thence the deposit spreads to the intra-acinous connective tissue round the affected vessels, ultimately reaching and affecting the tissue between the lobules and leading to confusion of their outlines. The connective tissue swells into homogeneous columns which split readily into flakes like hepatic cells, and which, in section, look like masses of degenerate cells or even whole lobules. Careful examination (p. 86) will, however, reveal between the lardaceous masses the liver-cells more or less atrophied and pigmented, the external especially being infiltrated with fat. These changes are beautifully shown if a very thin section be dehydrated in absolute alcohol, stained in an alcoholic solution of alkanet, decolorized in alcohol acidulated with hydrochloric acid, washed in water, tinted with acid hæmatoxylin, washed in water, colored with solution of iodine and iodide of potash, once more rinsed in water, and then mounted in glycerin; the fat is bright red, lardaceous substance brownish-red, liver-cells yellow, and nuclei dark grayish-blue. The fatty liver-cells show up clearly between the lardaceous masses, especially if a condenser is used (Orth).

Lardaceous Degeneration of the Kidneys.

The kidneys suffer frequently from this change, the spleen and liver being, as a rule, more markedly affected; but sometimes the degeneration appears to commence in the kidneys. Albuminuria being one of the most constant signs of this change, it is generally classed as one of the varieties of "Bright's disease."

The combination of lardaceous and fatty changes is exceedingly common in the kidney, the latter being to some extent secondary to the former, but the two bear no constant or proportionate relation. Further lardaceous change is frequently combined with the signs of inflammation, both interstitial and parenchymatous: the nature of the relation being sometimes obscure, it has been held that the nephritis causes the lardaceous change, that the lardaceous change causes the nephritis, and that both are concomitant results of the same cause.

NAKED-EYE CHANGES.—These are made up of the appearances characteristic of the lardaceous substance, of those due to fatty degeneration of renal epithelium, and of others due to inflammatory processes.

At first the changes are microscopic only; then the staining of thin

sections with iodine will show here and there a Malpighian body as a brown dot, the kidney being still normal to the naked eye, or perhaps pale, yellowish, and slightly softened. As the disease advances the organ enlarges, the cortex increasing chiefly. The surface is to the naked eye smooth, and the capsule separates readily. The enlarged cortex is remarkably pale and anæmic, and has a peculiar translucent, homogeneous, wax-like appearance. Its consistence is hard and firm. A few scattered vessels may be seen on the surface, and the bases of the pyramids sometimes exhibit increased vascularity. If iodine be poured over the cut surface, the Malpighian bodies and the arteries of the cortex become mapped out almost as clearly as in an artificial injection. The enlarged Malpighian bodies may indeed usually be seen as glistening points before the iodine is applied. Frequently, the homogeneous appearance of the cortex is interrupted by minute, opaque, yellowish-white lines and markings; these are produced by the fatty changes in the epithelium of the tubes, which so commonly occur in the later stages of the affection. Ultimately, the capsule becomes more or less adherent, and slight irregular depressions make their appearance upon the surface of the organ: the latter are due to atrophic changes in some of the tubes. If, as usually is the case, the process is associated with an increase in the intertubular connective tissue, the atrophy may render the organ even smaller than normal.

Fagge found about one-fourth of sixty cases from Guy's Hospital to weigh 20 to 27 ozs. The kidneys presented the appearance of the "large white kidney" (*q. v.*), but yielded the color-reactions of lardaceous degeneration; it is therefore necessary to examine all large white kidneys with iodine. Microscopic examination shows all the appearances of chronic parenchymatous inflammation plus those of lardaceous change. It is here that the relation between the degenerative and inflammatory change is most doubtful.

HISTOLOGY.—The degeneration usually begins in some of the capillary loops of certain Malpighian bodies, then all the loops become involved, and the change extends to the afferent arteries, the capillary network around the tubules, the arteriolæ rectæ of the medulla, and in advanced cases to the intertubular tissue, and even to the tunica propria of the tubules.

It is doubtful if the epithelium ever undergoes lardaceous change. The distribution of the change may for long be very irregular.

It begins in the subendothelial connective tissue, the endothelium remaining sound, and spreads to the media in arterioles, the muscular fibres either atrophying or undergoing the change; thus a homoge-

FIG. 22.

Lardaceous Degeneration of a Malpighian Tuft and Small Artery of the Kidney, showing the thickening of the walls of the vessel, the enlargement of the cells of the circular muscular coat, and the homogeneous layer formed by the intima and longitudinal muscular fibres. × 200, reduced ⅓.

neous glistening layer of varying thickness (Fig. 22) is formed. The lumina of the vessels are finally obliterated, and a Malpighian tuft becomes a solid ball, bearing on its surface for a long time undegenerate epithelial cells of the capsule; they are brought out by ordinary staining reagents. From the Malpighian tufts and afferent vessels the degeneration spreads as above described, giving rise to the dots, streaks, and finally coalescent patches seen with the naked eye.

At first the tubes and their epithelium appear normal. Many contain the pale hyaline casts which appear in the urine. They are probably simple exudation-products, but, occasionally, they stain deep brown with iodine, and these have been supposed to consist of lardaceous substance formed by metamorphosis of the exudation-material; according to Ziegler, however, these casts do not exhibit the other reactions of lardaceous substance. As the change advances and the new material increases in amount, the blood-supply becomes more and more obstructed, and the tubes are subjected to actual compression, which, according as it is uniform or irregular, leads to their atrophy, and perhaps to their disappearance or to their dilatation into small cysts. The epithelium undergoes atrophy and fatty metamorphosis, producing the opaque yellowish streaks and patches above mentioned, but

this change varies much in its amount and distribution. Not uncommonly a parenchymatous nephritis is present, the tubes being distended with cloudy or fatty cells, and the intertubular tissue being more or less infiltrated with leucocytes (*large white lardaceous kidney*). In the later stages of the process there is almost always increase of the intertubular tissue, which, together with the disappearance of tubes, leads to shrinking and toughening of the organ, to adhesion of the capsule and irregularity of surface.

EFFECTS.—The first effect of this change is to obstruct the circulation in the cortex; hence the increasing pallor of this part. The arterial walls are so altered that fluids and albumen readily permeate them; and thus is produced the large quantity of urine, loaded with albumen, which characterizes the earlier stages of this affection; the polyuria is, however, not so great as in the granular contracted kidney, where the pulse-tension is much higher. It is unusual to find the heart hypertrophied in cases of lardaceous disease. As the arteries and the tubes become more obstructed the urine diminishes in quantity. The excretion of urea is less interfered with than in other forms of Bright's disease, and hence symptoms due to its retention seldom occur. Tube-casts are rarely numerous; they are for the most part hyaline or finely granular, though sometimes they are covered with fatty epithelium.

In advanced cases there is marked dropsy.

Lardaceous Degeneration of the Spleen.

VARIETIES.—The spleen is very liable to this change, and is usually one of the earliest parts to be affected by it. Two forms are generally described: 1, the **sago spleen**, in which the disease is limited to the Malpighian corpuscles; and 2, the **diffuse form**, in which the whole splenic pulp is implicated. Kyber speaks of the latter as "parenchymatous degeneration," and makes a third form, indistinguishable from it by the naked eye, in which the disease begins simultaneously in the Malpighian corpuscles and the pulp. He holds strongly that these forms do not pass into each other, and particularly that the parenchymatous form is not an advanced stage of the sago spleen.

HISTOLOGY.—In the **sago spleen** the change commences in

the capillaries and arterioles of the Malpighian corpuscles, and extends to the lymphatic sheaths of these vessels of which the corpuscle consists. In the **parenchymatous form** the degeneration begins in the neighborhood of the capillary veins of the pulp, and

FIG. 23.

Lardaceous Degeneration of the Spleen ("Sago Spleen"): part of an altered Malpighian corpuscle, *a*, with the adjacent normal splenic tissue, *b*. The canals in *a* are degenerate vessels. × 200.

spreads thence to the trabeculæ, cells, and arterial capillaries. The third form (**general degeneration,** Kyber) shows the lesions of both the above. Some observers express a doubt as to whether the cells undergo this change, but they probably do.

NAKED-EYE APPEARANCES.—The **sago spleen** is more or less enlarged; its weight and density are also increased. The cut surface is smooth, dry, and studded all over with small glistening sago-like bodies, varying in size from a millet to a hemp-seed, which are stained a reddish-brown color by the iodine solution. These may become so large as to occupy a large portion of the organ, although in earlier stages of the affection they are so minute that they can be seen only in thin sections of the tissue.

In the **parenchymatous** and **general forms** the organ often attains a considerable size, much larger than is met with in the sago spleen. It is remarkably hard and firm, and the capsule is tense and transparent. On section it presents a dry, homogeneous, translucent, bloodless surface of a uniform dark reddish-brown color. Thin sections can be readily made with a knife, the organ cutting like soft wax. The corpuscles, if affected, are not visible as in the former variety, being probably obscured by the surrounding pulp.

EFFECTS.—Anæmia and emaciation, owing to interference with the blood-forming function of the spleen.

Lardaceous Degeneration of Lymphatic Glands.

HISTOLOGY.—In the lymphatic glands the process much resembles that in the spleen. The small arteries in connection with the follicles of the gland are the earliest seats of the change, and from these it extends to the lymphoid cells. The follicle thus becomes ultimately converted into a small homogeneous mass.

NAKED-EYE APPEARANCES.—The glands are enlarged, and on section the minute wax-like bodies can often be seen scattered through the cortex. The cut surface is smooth, pale, and translucent.

EFFECTS.—The same as in implication of the spleen.

Lardaceous Degeneration of the Alimentary Canal.

The whole alimentary tract may be affected, but probably never primarily or alone. The change is frequently present with tubercular ulcers. The disease in this situation is very apt to escape observation, as it usually produces but little alteration in the appearance of the parts. The mucous membrane may look somewhat pale, smooth, translucent, and œdematous; in very advanced cases there may be some rigidity and thickening of the bowel-wall and ulcers—due, it is supposed, to tearing off by the passing food of rigid villi. But the effect of the application of iodine to the washed mucous surface is very characteristic. In the small intestine—perhaps the part most commonly affected—a number of small reddish-brown points appear over the whole surface of the membrane: these correspond to the intestinal villi, the arteries and capillaries of which have undergone the lardaceous change. In the stomach and œsophagus the vessels are similarly mapped out by iodine. The change in the intestine gives rise to serous diarrhœa, probably due to increased permeability of the degenerate vessel-walls; both absorption and secretion are much impaired; so implication of the alimentary tract has a grave general effect.

The Corpora Amylacea.

Corpora amylacea, or "amyloid bodies," have usually been looked upon as consisting of lardaceous substance; there appears, however,

with the exception of a certain similarity in their behavior with iodine and sulphuric acid, to be no connection between them.

They are round or oval bodies, formed of a succession of concentric layers, and are often changed to a deep-blue color by iodine, thus bearing, both in structure and chemical properties, a strong resemblance to granules of vegetable starch (Fig. 24); but sometimes the blue is exhibited only after the subsequent addition of sulphuric acid, and thus a resemblance is shown to the lardaceous substance. Many bodies, however, are colored green, or even brown, by these reagents. The green is due to their admixture with nitrogenous matters, which give a yellow color with iodine, and hence the combination yields a green. The greater the amount of nitrogenous matter, the more brown does the color become. They vary in size from microscopic granules to bodies which are distinctly visible to the naked eye, sometimes being as much as one or two lines in diameter. The larger are usually formed by the conglomeration of smaller granules, which are often enclosed by a common envelope.

FIG. 24.

Corpora Amylacea from the Prostate. (Virchow.)

They occur especially in conditions of atrophy or softening of the nervous system, the ependyma of the ventricles, the white substance of the brain, the choroid plexus, the optic nerve and retina, and the spinal cord being their favorite seats. The larger forms are met with most frequently in the prostate. The prostate of nearly every adult contains some of these bodies, and they may accumulate here to such an extent as to form large concretions. They are occasionally met with in the lungs and in mucous and serous membranes.

From their laminated structure these bodies would appear to be formed by the prcipitation, layer by layer, of some material upon the surface of the pre-existing particles. The material, however, does not appear to be that met with in lardaceous degeneration. The two processes are so different, both in the circumstances under which they occur and in the characters and seat of the morbid products, that they cannot be looked upon as analogous. Lardaceous degeneration is a general change, whereas the formation of the corpora amylacea is evidently of a local nature. The latter is often preceded by those local atrophic changes associated with advanced life, and appears to consist in the deposition of some material, probably

liberated in the tissues themselves, upon any free body which may exist in its vicinity.

The corpora amylacea, especially those occurring in the choroid plexus and in the lateral ventricles, are very liable to become calcified, and they then constitute one form of "brain-sand," which is so often met with in these situations.

CHAPTER VIII.

CALCAREOUS DEGENERATION.

DEFINITION.—*Calcareous degeneration* or *calcification* consists in the *infiltration* of tissues with calcareous particles. It is a purely *passive* process, the cells taking no part in it; the tissue is petrified, without alteration of its structure at the time, by earthy salts deposited from the blood; for their quantity greatly exceeds that present in healthy tissues. It is difficult to find a physiological type, but perhaps the deposit of earthy salts in the walls of the primary areolæ (see "Rickets") in a growing long bone may be regarded as such. Ossification is quite distinct from calcification, for in it everything points to life and growth; the cells are undergoing *active* changes, and are obviously concerned in receiving the salts from the lymph and combining them most intimately with the organic matrix.

ETIOLOGY.—Earthy salts in solution, chiefly the *phosphates* and *carbonates of lime and magnesia*, are brought to the part by blood and lymph, carbonic acid being probably the solvent. We have to determine why these salts should be permanently deposited in certain tissues, and we are at once struck by the fact that in the immense majority of cases the tissues affected are dead or dying. It is probable, therefore, that feeble nutritive activity and a retarded blood-stream are the excitants. Rindfleisch taught that carbonic acid escaped from the stagnating lymph-stream, and hence the precipitation of earthy salts; more recently others have held that calcification is due to a combination of these salts with certain albuminoid bodies and with fatty acids.

Much more rarely calcareous infiltration appears to be due to an absolute increase of calcareous salts in the blood, such as may be sup-

posed to occur in extensive caries and in osteomalacia. A portion of the excess is then deposited more or less widely in the tissues—first in the lymphatic glands and kidneys, more rarely in the lungs, stomach, intestines, dura mater, and liver. The deposit takes place chiefly in the connective and least active tissue of the organ, which, moreover, immediately surrounds the vessels—*e. g.* in the interlobular tissue of the lungs and the stroma between the glands of the stomach—but in the kidney the epithelium is infiltrated as well as the intertubular tissue. Analogous to this form of calcification is the deposition of the excess of urate of soda which takes place in gout. It is probable that in this case also the deposit occurs first in tissues in which the nutritive activity is most feeble. A certain amount of chalky—like fatty—infiltration may perhaps occur without marked impairment of function; but, as completely calcified parts are certainly dead, either the infiltration has the power to kill or it affects dying parts.

SEATS.—Diminution or extinction of vital activity being the predisponent, we find that calcification is very common as a senile change, affecting most frequently the arteries and hyaline cartilages other than articular. It occurs similarly in pathological tissues of which the life is feeble—*e. g.* in uterine myomata after the climacteric and in old scars. Lastly, dead tissues locked up in the body are very likely to become calcified—*e. g.* thrombi (*phleboliths*), caseous masses, the results of arrested tubercular inflammation, so common in lungs and lymphatic glands, and atheromatous patches in arteries; but the chief example of this is the occasional calcification of an entire fœtus retained, dead, in the abdomen after an extra-uterine fœtation (*lithopædion*).

NAKED-EYE APPEARANCES.—A calcified substance may be merely gritty, like fine sand, or of mortar-like consistence, or welded into a solid stony mass, cutting and breaking with an irregular surface, and usually presenting a yellowish or grayish aspect.

HISTOLOGY.—The calcareous particles make their appearance both within the cells and in the intercellular substance; they are much more frequent, however, in the latter situation. They are seen at first as very fine dust scattered irregularly through the intercellular substance (Fig. 25). They are characterized, when viewed by trans-

mitted light, by their opacity, black color, irregular outline, and solubility in dilute mineral acids, usually with evolution of bubbles of CO_2. They gradually increase in number, until ultimately large tracts of tissue may be converted into an opaque calcareous mass, in which the cells are enclosed and can no longer be recognized. These larger masses have a sharp black, irregular outline, and as the calcifi-

FIG. 25.

A Calcified Sarcoma: minute calcareous particles are scattered through the intercellular substance—on the left so thickly as to almost conceal the cells. × 200.

cation becomes complete acquire a homogeneous, glistening, semi-transparent appearance. The cells themselves are much less frequently infiltrated, being usually merely enclosed and obscured by the calcified intercellular substance. Calcareous particles may, however, make their appearance in the protoplasm, and, gradually increasing, convert the cell into a homogeneous calcareous body. Calcification of ganglion-cells alone is not uncommon in degenerative processes in the brain.

If the saline matters are dissolved out with a little dilute mineral acid, the structure of the part may be again recognized, unless, indeed—as is so often the case—it has been destroyed by some antecedent change.

EFFECTS.—A calcified part is dead, inert, and undergoes no further change. In this respect calcareous differs from fatty degeneration, in which subsequent changes invariably take place—either softening, caseation, or calcification. It differs also in its effect upon the tissue; for, unlike fatty metamorphosis, it does not cause annihilation of histological elements. The tissue is simply impregnated with calcareous matters, which have no other effect upon it than to render it inert; its vitality is destroyed, but its structure—in so far as the calcification is concerned—remains unaltered.

Calcification must thus be looked upon in many cases as a salutary lesion, the impregnation with calcareous matters preventing subsequent changes in the part. This is especially the case when it occurs in caseous tubercular foci, as it probably imprisons the cause of the disease most effectually. It is doubtful whether calcification of a tumor is any benefit to the patient, for the infiltration probably affects only dead or dying parts. On the other hand, as when affecting the arterial system, calcification may be attended with most deleterious consequences.

Calcification of Arteries.

Calcification of arteries, like fatty degeneration, may be *primary* or *secondary*. As a secondary change it is one mode of termination of atheroma (*q. v.*) and is constantly met with in the aorta and its branches and many other situations.

Primary calcification is essentially a senile change, a result of that impairment of nutrition which appears and increases as life advances, but much earlier in some than in others. The change is more or less general. It is associated with atrophy of the arterial tissues, and in some cases with fatty degeneration. It usually occurs in vessels of medium size, the arteries of the upper and lower extremities and of the brain being those most commonly affected. Its most common seat is the middle coat, where it commences in the muscular fibre-cells. The calcareous particles, deposited from the vasa vasorum, make their appearance at first around and within the nucleus, and gradually increase until they fill the cell, which becomes converted into a small calcareous flake. The process may go on until the muscular coat is completely calcified, or it may be limited to isolated portions of the coat, giving rise to numerous irregularly distributed calcareous rings and plates. These are best seen in vessels clarified in spirit and turpentine. From the muscular it may extend to the external and internal coats, until ultimately the vessel becomes calcified throughout.

The vessel thus calcified loses its elasticity and contractility; its lumen is diminished, and it is transformed into a hard, rigid, brittle tube—"pipe-stem artery."

It is strengthened against dilatation, but is predisposed to rupture; and in amputations great difficulty may be found in securing such vessels, ligatures cutting through them at once. The nutrition of

parts supplied by them is more or less impaired, and tubular calcification of the arteries of the lower limb therefore predisposes to "senile gangrene" (p. 42.)

CHAPTER IX.

PIGMENTARY DEGENERATION.

PIGMENTARY degeneration, or pigmentation, consists in an abnormal formation of pigment in the tissues.

Normally, many pigments occur in the body, and probably all are the results of cell-action upon hæmoglobin. Some of them pass out in bile and urine; others are deposited as normal constituents in cells, the best examples being the cells of the rete Malpighii (especially in the negro) and those of the pigment-layer of the retina. But pigmented cells occur normally in other than epithelial cells; especially in the cells of the choroid and iris, of the sclerotic (lamina fusca), and of the pia mater. Muscle also is pigmented, and yellow or brown granules may sometimes be seen in the heart.

Pathological pigmentations may be arranged under four headings, according as the pigment is derived: 1. Directly from hæmoglobin; 2. From the blood by cell-action; 3. From bile; 4. From extraneous substances introduced into the body.

1. **HÆMATIC PIGMENTS**, or those derived direct from hæmoglobin, are the commonest. Red corpuscles may break up, and allow solution of their hæmoglobin, either within (malaria, septicæmia) the vessels, which is uncommon, or after having escaped into the tissues owing to wound or rupture of the vessels, or to congestion or inflammation (*q. v.*) without any breach in the vessel-wall. All the latter causes of pigmentation are common; witness the frequency of bruises and apoplexies, of congestions from varicose veins, portal obstruction, and cardiac incompetence, and of stains after various inflammatory lesions.

Certain changes take place in an extravasation which are accompanied, when the blood-coloring matter soaks into the skin, by changes of hue—from the initial purplish through greenish to yellow, with which all are familiar after a bruise. Briefly, these changes are the

following: 1. Some of the fluid and cells are absorbed at once by the lymphatics. 2. The hæmoglobin is dissolved out of many red cells, and the stromata disappear—no doubt after fatty degeneration. A red fluid is thus formed which infiltrates the tissues, staining them yellow or brownish-red—cells more deeply than intercellular substance, membranous, or fibrous structures. The color-changes on the surface are owing to changes in this dissolved hæmoglobin, which is soon decomposed into hæmatin and an albuminoid body; part of the hæmatin is reabsorbed and appears in the urine as urobilin; the rest undergoes a change and is deposited as granular or crystalline hæmatoidin. 3. Many corpuscles simply shrivel into brownish granular masses of pigment—said to occur chiefly in "hæmatomata," or tumor-like collections of blood. 4. Many—according to some, most—red corpuscles, or the pigment-masses resulting from them, are taken up by leucocytes, which wander in large numbers into the extravasation, and are converted in them into hæmatoidin. The pigment thus formed may be deposited on the death of the cell, or it may be carried by the cell into the lymphatics, when it will probably be arrested in the nearest lymphatic glands, the lymph-paths of which will be found beautifully marked out by pigment; or it may pass through into the circulation and give rise to pigment-emboli of various organs.

Hæmatoidin appears to be closely allied to—according to some, identical with—the coloring matter of the bile, bilirubin, also a derivative of hæmoglobin. It exhibits similar reactions when treated with concentrated mineral acids, displaying the same variations of green, blue, rose, and yellow colors. It is insoluble in water, alcohol, ether, and in dilute mineral acids and alkalies; it is soluble in the caustic alkalies, giving a red color. It contains more carbon than hæmoglobin, and it also contains iron. It occurs in two forms—granular and crystalline—and both are of a very permanent nature, remaining for years unaltered.

The granules of hæmatoidin vary in size from the smallest particles to masses as large as a red blood-corpuscle. The larger are commonly irregular in shape, sharply defined, and glisten more or less. Their color varies from yellowish-red to brown or black; the older they are the darker they become. The smaller granules are usually dull and opaque. The crystals of hæmatoidin[1] are opaque rhombic prisms, usually of a beautiful yellowish-red or ruby-red color, sometimes ap-

[1] Hæmin crystals are not pathological; they are obtained by warming blood—even a very old stain—with strong acetic acid, a crystal or two of salt being added.

proaching to brown or black. They may also occur as little plates and fine needles, but these are less common forms (Fig. 26). They are in most cases so small that considerable care is required to recognize their crystalline nature under the microscope, and they may easily be overlooked as merely irregular granular masses. In some cases, however, they attain a larger size. They are more or less transparent, and present a shining, strongly refracting surface.

Fig. 26.

Hæmatoidin Crystals. (Virchow.)

Intensely black pigment, granular or crystalline, has been called *melanin:* it is probably merely hæmatoidin altered by age, so that it is darker and less easily soluble; it contains more carbon than recent hæmatoidin.

Whether hæmoglobin is converted into granular or crystalline hæmatoidin appears partly to depend upon the tissue in which it is situated, crystals being exceedingly common in some situations, as in the brain and ovaries, whereas in others, as mucous membranes, only granules are met with.

According to Kunkel, some of the pigment left by hæmoglobin is pure hydrated peroxide of iron.

As to the ultimate fate of extravasations:

1. Absorption may be, and in vascular parts often is, complete, or crystals or granules of hæmatoidin may be found by the microscope. 2. A yellowish, brownish, or blackish scar, from granular or crystalline pigment, may record the destruction of tissue by hemorrhage. 3. A collection of prune-juice or chocolate-colored fluid may long remain surrounded by a capsule of inflammatory tissue, often lined by layers of clot, more or less decolorized and organized (hæmatoma); the fluid contains pigment- and fat-granules and cholesterin crystals. 4. The fluid may be absorbed and the clot become completely decolorized and organized—a good example of which is seen in the so-called "membranous pachymeningitis." The process can frequently be watched in aseptic wounds. 5. A cyst, with more or less pigmented walls, containing clear fluid may remain, especially in the brain.

Rarely, destruction of red corpuscles and formation of granular masses of hæmatoidin occur within the vessels: this occurs chiefly in malaria. It is thought also that many of the granular masses in "melanæmia" may be formed by imperfect development of red corpuscles in the spleen.

Pigmentation, with hæmatic pigment, is very common, but, *per se*,

of little importance. The presence of pigment in or between the cells of a tissue can have little effect on the elements of their functions: any disturbance of these must be attributed rather to the conditions upon which the formation of the pigment depends. As evidence of antecedent conditions (hemorrhage, congestion, or inflammation), the presence of hæmatoidin may sometimes stand alone; *e. g.* after cerebral hemorrhage from capillaries crystals of hæmatoidin may alone remain: again, slate-gray discoloration of the intestinal mucosa points either to prolonged catarrh, or portal congestion of the vesical mucosa to chronic catarrh. Slate-gray discoloration, seen chiefly post-mortem on solid abdominal viscera, from the action of sulphuretted hydrogen (from decomposition) upon the iron of hæmoglobin, must not be mistaken for this.

2. **PIGMENT DERIVED FROM THE BLOOD BY CELL-ACTION.**—The chief pathological instance is found in melanotic warts, nævi, sarcomata, and carcinomata. The pigment lies in the cells more often than between them, is granular, and varies from yellow to black in color: statements vary as to whether or not it contains iron. It differs spectroscopically from all known blood-pigments.

FIG. 27.

Cells containing pigment. From a melanotic sarcoma of the liver. × 350.

The bronzing of the skin in Addison's disease is at present unexplained.

Variations in the normal pigmentation of skin occur during pregnancy and with various uterine troubles, in leucoderma and melanoderma; but no certain explanation of these, or of blanching of the hair from neuralgia or fright, can be offered.

3. **PIGMENTATION FROM BILE.**—The only well-established cause of this is obstruction of the hepatic or common bile-duct by catarrh, stone, or other cause. The bile secreted behind the obstruction is absorbed by the veins and carried over the body: it appears first in the urine, then in the conjunctivæ, and may ultimately tinge all tissues yellow or greenish-yellow ("jaundice" or "icterus"). It may occur in small areas of liver only from obstruction of small bile-ducts in cirrhosis. The pigmentation is usually due to diffuse staining: rarely granules and even crystals of bilirubin are found, especially in *icterus neonatorum.*

With regard to the slight jaundice that occurs in septicæmia and malignant forms of acute infective fevers, no obstruction can be demonstrated in the ducts, and there often appears to be more or less suppression of bile. The theory has been propounded that bilirubin is formed by decomposition of the hæmoglobin in the blood, but this explanation is disbelieved by many.

4. **PIGMENTATION BY EXTRANEOUS SUBSTANCES.**—The best examples are those of *tatooing;* of *argyriasis*, caused by prolonged administration of salts of silver (the skin becomes permanently brownish-gray, more or less deep from deposit of silver in its intercellular substance); and of colliers' and knife-grinders' lungs, described in the next section.

Dead tissues are frequently discolored—black or greenish-black or slate-gray—by the action of sulphuretted hydrogen: this must not be confounded with ante-mortem pigmentation.

Pigmentation of the Lungs.

In no organs is pigment met with so frequently and in such large quantity as in the lungs, and much discussion has arisen as to its nature and origin. Its amount gradually increases with advancing age—the lungs of infants being free from it, whereas those of adults invariably contain considerable quantities.

This pigmentation of the lungs is due principally to the presence of carbon, and not of hæmatoidin. The carbon—derived from incomplete combustion of wood, coal, and other substances, and always present in varying quantities in the atmosphere—is inhaled, and the minute particles pass into the finest bronchi. Many are taken up by mucus-corpuscles, and may be seen as small black granules in the cells of the grayish-black sputum frequently expectorated in the early morning. Much of the carbon is thus eliminated by expectoration; but many particles pass into the air-vesicles, and here, their removal by this means being less readily effected, they gradually penetrate into the alveolar walls and interlobular tissue. Most of the pulmonary pigment is found in these situations, either within the connective-tissue cells or free among the fibres (Fig. 28).

According to Tyndall, exhaled complemental air is free from particles. How the carbon-particles reach the alveoli is not obvious: they can be carried by the air only so far as it is tidal or comple-

mental. Any cilia would work against the descent of the particle and its carrier cell; and the rarity with which empyemata from perforation putrefy would show that septic organisms rarely get as far as the alveoli.

The means by which the particles of carbon penetrate the walls of the air-vesicles and make their way into the interalveolar tissue has

FIG. 28.

Pigmentation of the Lung, from a woman æt. sixty five, with slight emphysema: Showing the situation of the pigment in the alveolar walls and around the blood-vessel *v*. × 75.

been thus explained by Klein:[1] The branched connective-tissue cells of the alveolar walls send a process, or a greater or less portion of their body, between the epithelial cells of the alveolus into the alveolar cavity. As these connective-tissue cells lie in the serous canals which constitute the commencement of the perivascular lymphatics, it is easy to understand how these openings in the alveolar walls (pseudo-stomata) may become sufficiently distended to allow cells and other substances to pass through them from the alveolar cavity into the interalveolar tissue. When once the carbon has made its way into the interlobular tissue, some of it is taken up by the fixed cells in this situation, whilst that which is not thus detained passes on to the lymphatics, and is deposited in the bronchial lymphatic glands, where the black particles are also visible.

Closely allied to this physiological pigmentation of the lung from the inhalation of carbon are those morbid conditions which result from the inhalation of particles of coal, stone, iron, and other substances, of which the lungs of miners, stonemasons, and grinders afford frequent examples. Here also minute particles enter the bronchi, penetrate the walls of the alveoli, and are deposited principally in the in-

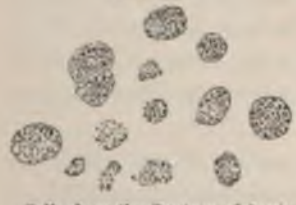
[1] "Anatomy of Lymphatic System of Lungs," *Proc. Roy. Soc.*, No. 149, 1874.

terstitial tissue. In the case of miners—in which this is most common—the particles of coal enter the lungs in such large quantities as to give to them a uniform dark, black color (*anthracosis*). In stonemasons, grinders, etc. the lungs also become deeply pigmented, although to a less extent than those of miners.

The black color of the lungs in these cases, however, is not entirely due to the presence of the inhaled substances, but partly to that of hæmatoidin. The irritating particles inhaled set up inflammatory changes in the bronchi and pulmonary tissue, causing chronic bronchitis, chronic catarrhal pneumonia, and a large increase in the fibrous tissue of the lungs, which thus ultimately become consolidated, tough, and fibrous, whilst ulceration, starting from the bronchi, produces cavities ("colliers'" and "knife-grinders' phthisis," etc.). Owing to these structural changes there is a considerable escape of red corpuscles from rupture of capillaries or inflammatory exudation, and hence a large formation of pigment, to which much of the dark color of these lungs must undoubtedly be ascribed. The lungs of stonemasons and grinders are, like those of miners, deeply pigmented, though to a less degree; but the black color in the former cases cannot be entirely accounted for on the supposition that it is due to the presence of inhaled particles.

Pigmentation of the lungs from the presence of hæmatoidin occurs as the result of many other morbid conditions, many diseases of these organs being attended by the formation of pigment. In chronic phthisis, pigmentation occurs, partly as the result of the inflammatory process, and partly from the obstruction of the vessels caused by the new growth: lines of pigment are constantly seen surrounding the nodules of consolidation. In acute croupous pneumonia the blood which is extravasated into the air-vesicles, and which in the early stages gives to the expectoration a rusty or prune-juice color, subsequently becomes converted into pigment, and the sputum becomes of a grayish-black, the pigment-granules being visible in the newly-formed cells. The cells met with in the sputum of bronchitis also contain granules of pigment (Fig. 29); and pigmentation plays an important part in the condition of the lungs known as brown induration (*q. v.*).

Fig. 29.



Cells from the Sputum of Acute Bronchitis, showing the minute granules of pigment within the cells. Some of the cells also contain a few fatty molecules. × 400.

Pigment in the lung usually occurs as black irregular granules; it is rarely met with in crystalline form. In all cases in which it is found in any quantity in the lung it is found in the bronchial glands also. It is taken up by the lymphatics, and, like the inhaled carbon, becomes arrested in its passage through these glands, where it remains permanently.

CHAPTER X.

NUTRITION INCREASED.—HYPERTROPHY.

THREE conditions must now be considered—**Hypertrophy, Regeneration**, and **Tumor-formation**—which have this in common: that in each the nutritive exchange of certain cells is so disturbed that formation exceeds waste, and growth results, just as in the physiological state. Pathological growth occurs in obedience to the same laws as physiological. In hypertrophy and regeneration the structure and function of the mother-tissue are retained, and no line can be drawn between pathological and physiological tissue-formation; but in tumors the disturbance results in the formation of a mass of new tissue, which fulfils no physiological purpose, which is always a morphological, and is frequently a structural, variation from the type of the part.

Normal growth depends upon—1. The inherited tendency of the cells to grow; 2. The supply of food; and 3. The amount of waste. Pathological new-growth will be due to abnormality of one or more of these factors.

HYPERTROPHY.

DEFINITION AND VARIETIES.—Hypertrophy means increase in size due to enlargement or multiplication of the normal constituent elements of a part or tissue, all being affected proportionately; so that external form and minute structure are alike preserved—*e. g.* hypertrophied heart from valve disease or kidney after loss of its fellow. This is **true** hypertrophy, and is accompanied by increased functional power. The terms **false** or **pseudo** hypertrophy indicate that the enlargement of an organ or part is due to overgrowth of one set of elements, often at the expense of another. It is the

connective tissue which generally becomes excessive, whilst the higher tissues atrophy—*e. g.* pseudo-hypertrophy of muscle. In these cases functional power is diminished. Both true and false hypertrophy may be extensive, involving one or more limbs; the latter when localized, gives rise to the "hyperplastic tumors." Hypertrophy is said to be **simple** when due to increase in **size** of the elements of a part; **numerical,** when to increase in their **number.** The latter is called also **hyperplasia.** These two forms are comparable to simple and numerical atrophy. In all hypertrophies hyperplasia is constant, and may be the sole cause of enlargement; but simple enlargement of cells may occur in each tissue, and is frequent in muscles and glands. In the great example of physiological hypertrophy—the gravid uterus—it is very marked, some fibres reaching seven to eleven times their normal size.

ETIOLOGY.—In many cases the causes are unknown. Often we cannot say whether a given hypertrophy is due to excessive vital energy of the cells of the part, to the setting aside for its embryonic rudiment of too large a number of cells, to diminution of the resistance to growth, to an ampler food-supply, or to diminished waste.

The clearest cases are those in which there is obviously an **increased supply of food.** For hypertrophy to occur, hyperæmia must be prolonged or frequently repeated; also, the cells of the part must possess ability to grow, for apparently no hyperæmia would prevent a thymus from atrophying or cause hyperplasia of adult ganglion-cells; and, finally, action is necessary to active assimilation in the working tissues of the body—muscle and gland (see p. 23). The following examples seem to fall under this head.

Repeated hyperæmia from slight injuries causes the thickened epithelium on the laborer's hand, and a corn arises similarly. Increased blood-supply to a limb may cause lengthening of a bone, of which an epiphysis remains ununited, as has been seen in large ulcers, caries, necrosis, etc. The soft parts increase secondarily. The hypertrophied spleen of intermittent fever and the thyroid in endemic goitre (Klebs) are due to active hyperæmia, perhaps excited by the presence of organisms. Exophthalmic goitre has been attributed to vasomotor paralysis from disease of the ganglia, but it is doubtful if it would result from such a lesion (p. 27).

When muscle contracts frequently against an increased load, it hypertrophies—as is seen in training—unless the load is *too* heavy,

when atrophy may result. Frequent contraction alone is insufficient, as is shown by hands used actively but not forcibly, by hearts after years of palpitation, by bladders after the frequent micturition of pyelitis. But insert an obstruction in the circulation or in the urinary passages which the heart or bladder can overcome, and hypertrophy begins. Examples of these **compensatory** hypertrophies are afforded by the heart in early stages of valve disease, the bladder in stricture of the urethra, the intestine just above a permanent stricture, a vein in aneurismal varix, or any vessel through which an abnormal quantity of blood is forced.

When an organ is removed or prevented from functionating, other organs which take on its work hypertrophy, receiving the blood which should have supplied the diseased organ as well as their own. This is best seen in the kidney, rarely in the testis and lung. Removal of one submaxillary would not cause hypertrophy of other salivary glands; this would occur only from more frequent stimulation of their secretory nerves, which probably produces the large submaxillary glands seen in epithelioma of the tongue. But the kidneys are under nerve-control to a much less extent; they seem to be excited to secrete by the presence in the blood of material suitable for their secretion, and hypertrophy naturally results from continued greatly increased supply of blood containing excess of urea, etc. Enlargement of lymphatic glands has been noted after removal of the spleen. Increased weight thrown on a bone causes thickening of it—*e. g.* of the fibula in ununited fracture of the tibia.

Diminished waste is, apparently, not a common cause of hypertrophy. An example often quoted is the subinvoluted uterus, the bulk of which is made up of hypertrophied muscle and connective tissue with thick-walled vessels, but it is doubtful to what extent chronic inflammation is responsible in these cases. Hair and nails uncut and unopposed teeth grow till their vessels supply only nutriment enough to maintain them in their finally attained condition. The sclerosis of bone produced by small doses of phosphorus, the increase in size and strength of animals treated with small doses of arsenic, and the invigorating effect of this drug upon Styrian mountaineers, may perhaps be explained by diminished waste.

The **removal of resistances to growth** is difficult to ascertain. It seems to be a factor in the production of such deformities as "knock-knee" (*genu valgum*): here excessive pressure is thrown on the outer articular surfaces of the femur and tibia, whilst the

weight borne by the inner surfaces is less than normal, and they, consequently, grow excessively. Many **scleroses** or hypertrophies of connective tissue follow upon atrophy of the essential elements of the organ: the natural resistance between the two tissues has been removed (see p. 131).

There remains certain cases in which the etiology is even more doubtful than in the above. Firstly, cases of **true giant-growth** —increase in length, rather than in breadth, being implied; hypertrophy of the whole body (giants); of half the body (rare); of whole limbs or of parts of them, as fingers and toes. Such parts are, on dissection, normal except in size. Secondly, cases of **false giant-growth,** in which the connective tissue alone is increased, the part being often misshapen; lymphatics are often dilated, even to cysts, and the blood-vessels may be nævoid. Examples are met with especially in the lip (**makrocheilia**), tongue (**makroglossia**), and lower extremity. Hypertrophy of non-working tissues would naturally result from an excessive, even slow and impure, supply of blood and lymph. In some of the above, which are congenital or appear soon after birth, there may be **excessive vital energy** or **too large a number of the cells** forming the rudiment of the part or tissue.

Nothing is known of the causation of senile hypertrophy of the prostate, nor of the enormous but rare enlargement of the female breast which may occur at puberty.

CHAPTER XI.

REGENERATIVE PROCESSES IN TISSUES.

Destruction of tissue-elements has frequently been described in earlier chapters as the result of injuries and various degenerative and inflammatory processes. We must now briefly state how such losses are repaired. It has already been said (p. 29) that cells of one embryonic layer always produce cells of tissues originally developed from that layer; and it is apparently true also that true regeneration of a tissue occurs only from cells of that tissue—muscle from muscle, epithelium from epithelium. Any form of connective tissue may, however, give rise to any other form—areolar tissue, bone, cartilage, etc. With regard to the origin of these tissues from leuco-

cytes, the latter must, when we consider their sources, be considered as connective-tissue corpuscles.

The regenerative processes which may go on in adult mesoblastic tissues are still imperfectly known. Their reproductive energy has been supposed to be limited to molecular repair. But it is certain that the cells of most adult tissues retain the power of multiplication, though it may not be manifest under normal conditions. This is probably owing to the facts that the blood-supply they receive is sufficient only to maintain them in *statu quo*, and that the resistances opposing growth, such as pressure within the tissue, are now equal to the force with which they tend to multiply. Loosen the intercellular pressure by wound or by destruction, and absorption of elements and multiplication of cells round about begins. Such injuries usually increase the blood-supply.

So far as investigation has yet gone, the nuclear figures described at p. 28 have been found in each tissue to form the first stage of division of cells.

As no extensive regeneration occurs without the formation of new vessels, we shall first state what is known concerning their production.

Vessels.

The formation of new vessels has been studied chiefly in the tadpole's tail, in sections of healing wounds, and in teased preparations of granulation-tissue. At the end of the second day after the infliction of a wound, and later, solid pointed processes are seen projecting from cells forming the walls of capillaries; they increase in length and join similar processes from other capillaries, or occasionally processes of branched connective-tissue corpuscles. At first very fine, the processes gradually widen and become hollow, and thus an anastomosing set of vessels (*intra*cellular channels) is produced. At this time a few nuclei are seen in their walls, the result of division of the original cell-nuclei, but nitrate of silver does not show the lines of union of individual endothelial cells. These develop subsequently. The process corresponds with that observed in the embryo (with the exception that no red corpuscles form in the cells), and is the same in the healing of wounds, in new growths, and in reproduction of lost parts.

Two much less certain modes of origin of vessels are described. (1) In granulation-tissue. Thiersch states that lymph-streams issuing

from the vessels form channels between the loosely-connected cells, which ultimately communicate with vessels and fill with corpuscles. Observations of Birch-Hirschfeld support this view. (2) Spindle-cells in granulation-tissue are said so to arrange themselves as to form canals which communicate with vessels. It is probable that they are really collected round a bud from a vessel (Ziegler).

As in the embryo, the new vessels may increase in size with the demands made upon them, muscular and fibrous coats being formed by cells which apply themselves around the original tube.

Adult vessels may increase greatly in size and thickness, as is seen in the gravid uterus and collateral vessels of a limb in which the main trunk has been tied; such vessels generally become tortuous as well as wider. Increased flow through the vasa vasorum is always present.

Common Connective Tissue.

This is the most frequent seat of new formation of all kinds—hypertrophy, tumor-formation, and regeneration. With regard to the latter, it seems that loss of substance is made up for from two sources—the fixed connective-tissue corpuscles and wandering leucocytes. Formerly all new cells in the tissues were regarded as products of connective-tissue corpuscles. Then it was thought that adult connective-tissue corpuscles were incapable of growth, and that almost all new fibrous tissue was of inflammatory origin, and hence many pathologists regard all scleroses as inflammatory. Now the happy mean seems to have been reached, and it is held that both connective-tissue corpuscles and leucocytes may form fibrous tissue. The difficulty in estimating the part played by each is extreme; but Senftleben's experiments (p. 252) on the cornea prove the regenerative power of connective-tissue cells, and Ziegler's experiments with glass chambers (p. 260) seem to demonstrate with equal clearness the development of white blood-corpuscles. Some authors are inclined to think that scar-tissue of inflammatory origin is only temporary, being slowly replaced by tissue resulting from the regenerative processes going on in the neighboring connective-tissue cells. The tendency of scars is to become fainter. The denser kind of connective tissue as a rule results from inflammation.

Adipose Tissue.

This is merely connective tissue of which the cells are infiltrated

with fat. Newly-formed connective-tissue cells may certainly thus become infiltrated—*e. g.* in pseudo-hypertrophic, and to a less extent in infantile, paralysis; but inflammatory tissue, as a rule, remains free from fat.

Cartilage.

A wound or breach in cartilage is generally repaired in the first instance by scar-tissue, which may be replaced later by hyaline cartilage formed from the perichondrium and by proliferation of neighboring cartilage-cells, the matrix being formed, according to Strasser, from the protoplasm of the cells. Often this replacement by cartilage does not occur. In cases of fractured rib-cartilage the fibrous tissue may ossify into a clasp of bone round the broken ends.

Bone.

The regenerative power of bone is considerable, and depends chiefly upon the periosteum, to a less extent upon the marrow. The process is best illustrated by the repair of a simple fracture.

Repair of a Simple Fracture.—During the first twenty-four hours an examination shows the broken ends of the bone lying in a collection of blood coagulated where it is in contact with the tissues, but fluid round the fracture. The bone-ends are sharp and jagged, the periosteum more or less torn and stripped off, the medulla more or less deeply ecchymosed. The injury to the vessels of the part excites exudation of fluid and of cells; the latter infiltrate the torn tissues, so that in three or four days they are found to have lost their characteristic appearance, being soft, pink, and gelatinous, as is best seen in the medulla. In fact, they are granulating, and the granulation-tissue increases in amount until the blood around the fracture has disappeared and the ends of the bones are imbedded in a mass of soft tissue. Not only do the periosteum and medulla give rise to this, but also other injured soft parts. From the third or fourth day certain large angular cells are seen close to the bone which play the part of osteoblasts. Here, as elsewhere, the source of the cells of the granulation-tissue after the effect of the primary injury has subsided is disputed, some referring their origin to leucocytes, others to the cells of the medulla and periosteum. Probably both contribute, but the effect of irritation (mobility of fragments) in causing free formation of callus is in favor of a large share for the leucocytes. This soft tissue is found

in plenty about the tenth day, when it is difficult to distinguish the periosteum, which is swollen and infiltrated with cells like other parts. Now, the granulation-tissue becomes firmer, and at about the fourteenth day the periosteum can again be seen covering a spindle-shaped swelling, which extends beneath it for some distance up and down the bone. As Billroth says, the ends of the bone are stuck into this spindle-shaped mass as if it were soft sealing-wax; there is a ring outside and a plug in the medulla. This uniting tissue is called the **provisional callus.** In animals it is generally converted into cartilage, but in man direct ossification usually begins in the third week. In man, however, when tolerable rest cannot be maintained, as in fractured ribs and many fractures in children, cartilage may be developed. It is always in greater quantity where the bone is thickly covered by soft parts, and rarely forms a complete ring in man. It is strongly developed in any angle or gap. Where the most perfect rest is obtained, as in fissures of the skull, little or no provisional (or permanent) callus is formed.

Ossification of the provisional callus begins in the angle between the periosteum and the bone, and extends thence beneath the periosteum and along the surface of the bone. The plug in the medulla ossifies a little later. At first the bone is soft and open in structure and easily picked off the shaft. Its canals are more or less vertical to the surface of the shaft, and continuous with abnormally wide Haversian spaces in the latter. Ossification begins round the vessels passing from the callus to the bone, the cells most distant from each assuming the shape of osteoblasts and becoming surrounded by or converted into bone. Osteoblasts inside each ring now lay down laminæ of bone until Haversian systems are formed. The callus is now intimately united with the original bone, and holds the ends firmly together. The medullary canal is blocked by bone and osseous buttresses fill up any angle. This complete ossification of the provisional callus is finished in man between the fourth and eighth weeks, according to the size of the bone.

So far the bony tissue has not been mentioned. The next step is to unite the two ends directly by what is termed **permanent** or **definitive callus.** This is said to begin to form when the provisional callus has fixed the ends of the bones; but preparation for this union begins much earlier. The ends of the bones are to be softened into a tissue which can bridge over the gap, blend the two fragments into one, and finally ossify. A rarefying ostitis begins probably imme-

diately after the injury, and results in a round-celled growth which slowly eats away the walls of and enlarges the Haversian canals. Naturally this is a much slower process than similar infiltration of the soft parts. So long as the bones are moving on each other the granulations would have little chance of blending across the gap; but as soon as the fragments are fixed this union occurs, and ossification, running on to sclerosis, follows. It is probably not complete before the fourth month.

The final process in the union of a simple fracture is the rounding off of all prominences and the absorption of all unnecessary provisional callus. The completion of this may occupy years; but ultimately, in an accurately set fracture, the medullary canal may be opened up and most of the thickening around the shaft removed. Generally, the seat of fracture remains evident, but Billroth says that in some cases it cannot be recognized.[1] The analogy between the repair of bone and the repair of ordinary connective tissue, as described under "Healing of Wounds," scarcely needs pointing out; ossification of the scar-tissue is the main difference.

Repair of compound fractures is effected by the ossification of granulation-tissue, either directly or after its conversion into fibrous tissue. But suppuration, implying more or less destruction of the new tissue, and often necrosis of soft and hard tissues, greatly delays the process. (For separation of sequestra, see p. 42.) Even where compound fractures become simple from the first by union of the wound they are often much longer in healing: the reason is not evident.

Muscle.

A wound in a muscle as a rule gapes widely and heals by granulation. In some parts, as the tongue, retraction is prevented, and union by first intention occurs readily. The protoplasm escapes through the opened sarcolemma, and leucocytes penetrate for some distance between the fibres. Ordinary scar-tissue develops from the granulation-tissue and unites the ends of the muscle. New cells are now produced by the muscle-cells on each side of the scar, and they invade and may eventually replace the cicatricial tissue. Kraske says that new muscle-cells are produced only by multiplication of the nuclei of the old. Each nucleus becomes surrounded by a spindle-shaped mass of protoplasm and divides to form muscle-fibres. In some cases no regeneration is evident.

[1] 10th ed., p. 244.

Regeneration occurs more frequently to repair losses from degeneration, such as that which occurs in acute febrile diseases, especially typhoid. The new cells are believed to spring from small elements lying between the original muscle-fibres or by splitting of the old cells from end to end.

Involuntary muscle-cells multiply also by division. There is some doubt as to whether these may not arise from connective-tissue corpuscles.

Nerve-Cells and Nerves.

Nothing is known of a regenerative process among ganglion-cells, and many think that none occurs in adult life. An ordinary scar is all that is known to replace destroyed ganglionic tissue.

When a nerve is cut across union takes place readily by scar-tissue if the ends are brought together; and, as a rule, function is restored in the course of time even when a considerable piece (in some cases nearly two inches) has been excised.

After division, myelin escapes up to the nearest nodes of Ranvier, and blood is extravasated between the fibres and in the sheath. Then leucocytes infiltrate the ends for a short distance, rendering them bulbous: the soft parts are similarly infiltrated, and a mass of granulation-tissue soon unites the ends. Later, this develops into ordinary scar-tissue.

Beyond the degeneration of a few fibrils no other immediate change occurs in the central end. In the peripheral end changes may be noted after twenty-four hours; they lead to destruction of the nerve. The following account is taken from Ranvier:[1] In warm-blooded animals, after twenty-four hours the nuclei in the primitive sheaths are found enlarged and the sheath is everywhere visible; then protoplasm accumulates round the nuclei, at the nodes and other points, replacing the medullary substance. On the third or fourth day these protoplasmic masses are so large as to interrupt completely the sheath of Schwann at many points. At the same time the nuclei are seen to have multiplied once or twice. A little later and almost all myelin has disappeared, the axis cylinders are broken into short segments which may finally go, and nothing remains of the peripheral end of the nerve but the primitive sheaths, full of clear granular protoplasm and distended at intervals by nuclei which are abnormally frequent. Some drops of myelin persist. A few fibres do not undergo degeneration. They are thought to have sprung from other undivided

[1] *Leçons, etc.*, 1878, as quoted in Quain's *Anatomy*.

nerves lower down, and to be taking a recurrent course in the divided trunk. These fibres degenerate in the central end. These changes are said to begin in the muscle-plates in motor nerves, but they occur practically at the same time throughout the peripheral ends. They are generally complete in fourteen days, The nerve is now gray and shrunken; its fibrous tissue overgrows, causing further wasting and induration.

No regenerative changes occur for four or five weeks. Then it is found that the axis cylinders of the central end are dividing into two bundles (which again divide several times) or into several, and that these small new axis cylinders are finding their way through the scar-tissue into and between the old primitive sheaths. Growth of the axis cylinders always begins from a node next above or close to the section, where the sheath of Schwann is bulbous. A cross-section of the peripheral end at about the eighth week shows small medullated and non-medullated nerves among the old primitive sheaths, full of protoplasm. The course of these new fibres is very irregular, especially through the scar, where they may even loop back. At first non-medullated, they acquire later sheaths of Schwann, with nodes of Ranvier, which are at first placed at short intervals, as in young nerves. In the scar primitive sheaths even are at first wanting, but they ultimately form from the surrounding connective tissue.

Many months, or even a year, may pass before function is restored, a shorter time being required in sensory than in motor nerves, and it is supposed that during this time the axis cylinders are slowly finding their way along the nerve. The time varies with the length of nerve beyond the division and with the distance between the ends. The number of axis cylinders produced in this process is much greater than that of the nerves destroyed. It seems probable, therefore, that many atrophy, but their further history is not known.

Cases occur in which restoration of sensation takes place within a few days of the division of a nerve. The explanation is probably that communicating nerves take on the function of the divided one; but Ross and others think that, if the ends are kept in contact, "immediate" union of the axis cylinders may occur.

When union does not occur, and after removal of the peripheral part, the proximal end becomes bulbous (see p. 170).

Epithelium.

Epithelium is always derived from pre-existing epithelium by simple division of the cells. This is shown by the fact that it always spreads

in from the edge of an ulcer, unless islets of the rete have been left undestroyed in the midst of the granulation-tissue.

The epithelium of the skin and mucous membranes and of many glands is being destroyed and replaced throughout life—sometimes very rapidly, as in catarrhs of mucous membranes and of the kidney (acute nephritis).

But if all the cells of an acinus or tubule of a gland be destroyed, there is probably no reproduction of epithelium. A wound of a gland, with or without loss of substance, heals by scar-tissue, which is permanent.

Regeneration of nails and hair is frequent.

Healing of Wounds.

The union of most wounds and the repair of losses of substance are effected primarily by the formation of more or less scar-tissue—*i. e.* by the development of new vessels and new connective tissue. Subsequently more or less regeneration of the injured tissues may take place in the modes above described. Several modes of healing are described, but they are fundamentally the same. They are—(1) Immediate union; (2) Union by first intention; (3) Healing by second intention or granulation; (4) Healing under a scab; (5) Union of two granulating surfaces.

Immediate Union.—Described by Macartney in 1838, the occurrence of the process has been confirmed by Paget and by Thiersch, who states that it occurred in wounds inflicted on the tongues of animals. The union is said to be effected by a blending of the practically unchanged surfaces of the wound, no lymph intervening as a bond. It is complete in twenty-four hours, and no scar results. Most pathologists deny that such a process ever occurs. They believe that lymph, possibly only in microscopic quantity, invariably forms the first bond of union. With them the next form is the speediest mode of healing possible.

Union by First Intention.—This generally occurs in well-treated incised wounds. It is prevented if the surfaces are not accurately brought together, being left gaping superficially or separated in their deeper parts by foreign bodies, blood, or fluid exudation in any quantity; by movement of the surfaces on each other; by sloughing of the surfaces; or by irritation of any kind which excites inflammation going beyond the fibrinous stage. When these conditions are avoided by careful arrest of hemorrhage, cleansing, drainage, apposition, pro-

vision for rest, and prevention of septic and infective inflammations, the following changes take place: The capillaries become thrombosed up to the nearest collateral; in tied or torsioned vessels the changes described at p. 220 set in. The injury inflicted by the knife was severe, but strictly localized and of very short duration. It excites free exudation of fluid and corpuscles. At first there are many red corpuscles in the discharge, but they rapidly diminish and the fluid becomes clear and deep yellow. The discharge escapes between the edges of the wound if it is small in quantity, or if large through channels purposely left. The fibrin contained in the exudation coagulates on the opposed surfaces, binding them together; it contains more or fewer leucocytes. It is this lymph which forms the "glaze" on wounds left open. The exudation diminishes greatly as the effect of the injury is recovered from. Microscopic examination after twenty-four to thirty-six hours shows the edges of the wound separated by a narrow band of small round cells; the tissues close to the incision are swollen and hazy, and more or less infiltrated with leucocytes. New vessels develop after the second day, and shoot across from side to side, converting the lymph into granulation-tissue (p. 260). This then goes on to the development of a scar (p. 261). The number of leucocytes about the wound varies with the amount and duration of the irritation; in some cases it is quite difficult to make out what holds the edges together. Thus in a herniotomy wound examined on the fourth day (Fig. 30) the line of incision was recognized almost solely by the fact that the fat on one side was adherent to the deeper layer of the cutis on the other; the two seemed to be in actual contact, and there was hardly any round-celled infiltration. The part taken by the tissue-elements in scar-formation is not yet determined. The older a scar is the more closely does it resemble the normal tissue.

FIG. 30.

×20
Union by First Intention: See text.

Union by Granulation.—When a wound cannot be brought together, or when union by first intention is prevented, this form will occur. Until union takes place a raw surface is necessarily exposed to some irritation. This, some think, keeps up a constant exudation of fluid and leucocytes from the new vessels, just as the original injury excited such exudation from the vessels of the normal tissue, and the leucocytes imbedded in a little intercellular substance become vascularized into granulation-tissue. Others say that after the primary severe irritation has subsided granulation-tissue is produced by multiplication of the neighboring connective-tissue corpuscles. However formed, the tissue increases in amount, either by continued infiltration with leucocytes or by multiplication of its own cells, or by both processes, until the wound is filled up to the level of the surface, when the granulations skin over, as described on p. 119. A granulating wound under ordinary dressings suppurates more or less freely, but one treated antiseptically and protected from irritation by the antiseptic employed discharges a serous fluid. A section through granulation-tissue shows on the surface a layer of small round cells with bi- or tri-partite nuclei, imbedded in a substance which is actually fluid superficially: this layer is breaking down into pus. Deeper are found fibroblasts (p. 261), and deeper still scar-tissue in all stages of formation. The thickness of the surface-layer and the amount of pus formed vary with the irritation to which the tissue is subjected. In some cases destruction equals or exceeds growth of granulations. Here again, therefore, treatment should be directed to the avoidance of all unnecessary irritation.

Fig. 31.

Union of Two Granulating Surfaces from a Breast-wound: The uniting material is in much greater amount than in Fig. 30.

Healing under a Scab.—In this form the exudation is small in amount and dries into a scab. It is not common in man except in

superficial abrasions. Formation of granulation- and scar-tissue occurs beneath it, as also does the inward growth of epithelium. When "skinning over" is complete the scab drops off. The dry scab is but slightly irritant in itself, and it does not putrefy. When ulceration spreads beneath a scab some ineffective agency is probably the cause. The process of scab-formation is sometimes imitated by closing wounds, often leading to cavities, with collodion, or allowing blood or tincture of benzoin on lint to dry and occlude the opening. Such treatment is, however, dangerous; for if septic or infective organisms have entered and excite inflammation, the absence of drainage will be most prejudicial.

Union of Two Granulating Surfaces.—When two surfaces have granulated as above described, they may be brought together; and frequently the two surfaces will blend, thus saving the time which would be required for filling up from the bottom. Free suppuration and imperfect drainage will prevent such union. This is the way in which abscesses should heal when their walls are allowed to fall together by evacuation of the pus.

Transplantation of Tissues.

John Hunter transplanted a cock's spur into its comb, and it has long been known that small pieces of the body, like the tip of the nose or finger, might unite if fixed in position soon after complete separation from the body. But accurate knowledge on this subject has been acquired only since Reverdin's discovery of "skin-grafting."

The tissues, as is well known, do not die when the body, as a whole, does. Portions of almost all tissues may be removed from one part or animal and transplanted to another part or animal without dying, if the conditions are suitable. These are—transference of the portion of tissue with sufficient gentleness and quickness to ensure that it is alive when transferred; close contact with the raw surface prepared for it; maintenance of its temperature; and the avoidance of all irritation, especially septic. The piece of tissue will, under these circumstances, become united by first intention to its bed, and will be nourished by lymph transuding from this surface until vessels shoot across into it. Naturally, those tissues bear transplantation best which are least highly organized and require the least nutriment.

Epithelium is the tissue which better than any other bears transplanting. Use is made of this in the operation of grafting, in which

small bits of *the superficial part* of the rete are placed upon a healthily granulating surface. They are nourished by the exudation at first, grow and adhere, forming centres whence epithelium spreads over the surface. The cells of the root-sheath of plucked-out hairs answer the purpose well. Granulation-tissue may be skinned over in this way, but unless scar-contraction accompanies the skinning over the cicatrix breaks down readily.

A piece of **skin** an inch square, freed from all fat, may be transplanted, and thus *ectropion* and similar deformities may be remedied.

Similarly, a bit of **mucous membrane**, usually obtained from a rabbit's conjunctiva, is transplanted in cases of *entropion*.

Cartilage and **periosteum**, especially when young, bear transplantation well (see pp. 130 and 133). So also do bits of **bone**. Macewen of Glasgow built up part of an ulna with bits removed from deformed tibiæ, and introduced the practice of replacing chips of the bone removed in the opening made by a trephine.

Pieces of **muscle** have been successfully transplanted, and part of the sciatic **nerve** of a bird has been substituted for a corresponding piece excised from another bird: the transplantation of nerve has been successful in man, so far as the mere healing-in of a portion of rabbit's nerve placed between the ends of a divided median, but time had not been allowed for restoration of function when the notice was published.

CHAPTER XII.

TUMORS.

DEFINITION.—The first notion which the name "tumor" conveys is that of swelling; but swelling may result from various pathological processes, and it is consequently necessary to exclude such swellings as do not conform to the idea which rises in the pathologist's mind when a swelling is described as a tumor. The features of this idea are—a formation of new tissue which is abnormal to the part; which disturbs its form, and differs from it more or less markedly in gross and in minute structure; which performs no physiological function; which tends to continuous growth, and is more or less independent of the general nutrition of the body; and which has not arisen from the causes or with the course of inflammation.

That tumors are formations of new tissue necessitates the rejection of all swellings due solely to retention of secretion (retention-cysts), or to extravasation of blood (hæmatoma); true hypertrophies must be rejected because, though they cause an increase in size, the shape, structure, and function are preserved. Finally, all inflammatory swellings, tumor-like products of infective inflammations (gummata, tubercle, farcy-buds, etc.), condylomata, localized œdemas and effusions—such as hydrocele—must be eliminated.

The definition of a tumor as an *atypical new formation* would separate the class from retention- and extravasation-cysts and from true hypertrophies; but many an inflammatory new formation, as callus or a condyloma, is atypical enough both in form and structure. Moreover, there is a whole group of tumors (sarcomata) which it is impossible to distinguish anatomically from the results of inflammation. It is therefore necessary to include in a definition of tumors something which shall draw the line between them and inflammatory products: this will be that their causes, modes of origin, and often courses, are different. We may say, then, that *a tumor is an atypical new formation, not the result of an inflammation.* As scarcely anything is certainly known of the causes of tumors, it is impossible to frame a complete, positive definition of a tumor which shall not be disputed by many. False hypertrophies, especially such as affect limited areas (*e. g.* accumulation of fat on the buttocks of Hottentots), are closely allied to simple tumors and specially difficult to separate from them.

DEVELOPMENT.—The nutrition of tumors is not regulated like that of normal tissues. When the body gets thin a fatty tumor wastes little or not at all, and malignant growths often grow luxuriantly when their victims are emaciating greatly. With this fact it may be noted that tumors have no nerves, though the relation of nerves to nutrition is as yet little understood.

A tumor consists of cells formed by multiplication of pre-existing cells, and here, as elsewhere in nature, the characters of the parent are handed down to the offspring. In other words, a tumor belongs histologically always to the same class of tissues as the cells from which it springs (see p. 29).

In development and structure the tumors resemble the normal tissues: every pathological growth has its physiological prototype. The resemblance, however, is by no means complete, for, as indicated in the definition, they are always more or less **atypical** in their structure.

As a rule, the difference between the normal and abnormal tissue is such that with the naked eye one can tell roughly where the one begins and the other ends.

The histological processes which give rise to the formation of a tumor are doubtful in the extreme. It is uncertain whether a tumor grows from a portion of the mature tissues or from a kind of "resting spore" of embryonic tissue, as suggested by Cohnheim (p. 133). Evidence of multiplication of normal tissue-elements round about a growing tumor is often obtainable, but it is difficult to tell what becomes of them, and Ziegler was inclined to think that most disappeared. A cancer-embolus in a gland almost certainly grows without any additions from the surrounding cells, and there does not seem to be any *a priori* reason why a fibroma or a sarcoma should receive any, either.

The elements from which tumors most frequently originate are those belonging to the **common connective tissue** and to the blood-vessels and lymphatic system with which it is so intimately associated. By common connective tissue is meant that tissue which in all parts surrounds the blood-vessels and is so universally distributed throughout the entire organism. This must be carefully distinguished from the special varieties of connective tissue—tendon, cartilage, bone, etc. In this common connective tissue we distinguish two kinds of cells—the stable or connective-tissue corpuscles, and the mobile or "wander-cells." Both are in intimate relation with the endothelium of the lymphatics, which commence as spaces distributed throughout the tissue. Further, the endothelium of both lymphatics and blood-vesssls closely resembles in its physiological functions the fixed cells of the connective tissue.

Connective tissue is said to give rise to tumors by multiplication of its cells, the part played by the two kinds being doubtful. Embryonic tissue results in small round cells with no limiting membrane and a large nucleus, lying in a scanty, semi-fluid, and faintly granular intercellular material. This tissue is often called "indifferent," as it is impossible to determine in this early stage of the growth what it will ultimately become—whether a fibroma, a sarcoma, or an enchondroma, etc.

This "indifferent" tissue now develops into that of the permanent growth, much in the same way as the immature connective tissue of the embryo develops into various connective-tissue substances—mucous tissue, fibrous tissue, cartilage, or bone. The embryonic tissue may undergo no higher development, the cells remaining round or

oval and the ground substance homogeneous; or the nuclei of many cells may multiply without division of the cells, forming giant-cells; or most of the cells may lengthen out into spindles, and perhaps here and there fibrillation, with disappearance of some cells, may occur. We thus get the round or oval-celled, myeloid, and spindle-celled sarcoma; also the fibro-sarcoma. General fibrillation with disappearance of most of the cells, mucous degeneration, chrondrification, or ossification of the stroma, may occur, forming fibroma, myxoma, chondroma, osteoma; or fat may form in the cells—lipoma. A combination of two or more kinds of structure may be met with in the same tumor, as a combination of sarcoma and lipoma, of enchondroma and myxoma, and so on. We are quite ignorant of the causes, apart from heredity—which exercises only a general influence—determining the ultimate character of the tissue.

Next to connective tissue, **epithelium**—surface and glandular—is the tissue from which tumors most frequently originate; and as from connective tissue are produced growths of the connective-tissue type, so growths originating from the epithelia preserve the epithelial type. *A priori*, it would be entirely contrary to evolution for them to do otherwise; and the great majority of observers state as the result of their observations that epithelium never arises but from epithelium. It is nevertheless believed by some that an epithelium-cell may by mere contact so influence a connective-tissue cell that it becomes epithelial, or *vice versâ*. This influence of one cell upon another is called "spermatic" (Creighton). The point has been carefully investigated by Ziegler with a negative result.

From the remaining tissues, **muscle** and **nerve**, the development of tumors is comparatively rare, and in the highest adult nerve-tissue it is doubtful if formative processes ever occur.

According to the similarity or difference which subsists between the new growth and the tissue from which it grows, tumors are divisible into two classes—**homologous** and **heterologous**. When the tumor resembles in its structure and development the tissue from which it *originates*, it is said to be homologous; when it differs, it is said to be heterologous. A cartilaginous tumor, for example, growing from cartilage, is homologous, but growing from any other tissue, as from the parotid gland, it is heterologous. This distinction is probably superficial, not real. If it be correct that tissue-types "breed true," the only even apparent heterology which we know to occur is the development of the different connective tissues from the same embryonic tis-

sue. In the example given cartilage does not arise from the essential epithelial cells of the parotid, but from the supporting connective tissue or from an aberrant bit of cartilage from the rudiment of the jaw (p. 148). Heterology, however, is not limited to the production of a tissue which is dissimilar to that from which it originates; a tumor is said to be heterologous (or **heterotopic**) also when it differs from the tissue in which it is *situated;* and this may occur without its being the direct product of the latter. It is heterology in this sense that is so characteristic of malignant growths. Cancers, for example, become heterologous owing to the growth and extension of the epithelium beyond its normal limits (see "Epithelioma," Fig. 64); and the same form of heterology obtains in the case of all growths originating from elements which have migrated or been carried from their original habitat, and have developed into a tissue differing from that in which they are situated.

RELATION OF THE TUMOR TO THE SURROUNDING TISSUES.—The relation of the tumor to the surrounding structures varies. In one case the tumor is circumscribed, merely displacing the surrounding parts, stretching and irritating their connective tissue; and this often forms a fibrous capsule around it by which it is completely isolated. The lipomata, fibromata, and enchondromata are usually thus encapsuled. In other cases the growth invades the adjacent structures. There is then no line of demarcation between the tumor and the surrounding parts; and although to the naked eye there may seem to be one, the microscope will show that the apparently

Fig. 32.

Scirrhus of the Mamma: Spreading margin; small-celled infiltration of the muscular fibre and adipose tissue in the neighborhood of the gland. × 200.

healthy tissues are infiltrated with a small round-celled growth (Fig. 32) into which the specific tumor-cells are advancing. The former is probably the result of tissue-irritation set up by the latter.

RETROGRESSIVE CHANGES.—A tumor very rarely disappears, and it thus differs from an inflammatory growth—*e. g.* a gumma. It may remain stationary or grow slowly or rapidly, and sooner or later it usually becomes the seat of retrogressive changes. The time at which these commence varies. As a rule, the permanence and durability of a tumor bear an inverse relation to the rapidity of its growth and to the inferiority of its organization. The more rapid the growth and the more lowly organized the tissue formed, the less its durability and the sooner do retrogressive changes occur. The carcinomata and sarcomata develop rapidly, consist for the most part of cells, and quickly degenerate; their elements are unstable and soon perish. Osseous tumors, on the other hand, develop more slowly, consist of a more highly organized tissue, have much greater stability, and are but little liable to retrogressive metamorphosis.

The retrogressive changes are similar to those met with in the physiological tissues. Deficient supply of blood is followed by **fatty degeneration** and its various terminations—softening and caseation. **Pigmentary, calcareous, colloid,** and **mucoid degeneration** also may occur. Tumors may become the seats also of **inflammation,** ulceration, necrosis, and hemorrhage.

CLINICAL COURSE.—Tumors are divided clinically into two great groups, the **simple** and **malignant.** A **simple tumor** is one which, as a rule, grows slowly and steadily, or, having attained a certain size, remains stationary. It consists of tissue approximating closely in structure to some normal adult tissue, and is generally surrounded by a distinct capsule out of which it can be completely shelled, for there is no infiltration of surrounding parts. After such removal it does not recur locally, and secondary growths in glands or more distant parts do not result from it. It interferes with health only mechanically, unless some accident, as inflammation, occurs in it. Tumors of the adult connective-tissue type generally pursue this course, and may reach a huge size.

A **malignant growth,** on the other hand, generally grows rapidly and tends to enlarge continuously; consists of tissue which is markedly atypical; is, as a rule, surrounded by no capsule, but progressively infiltrates the surrounding tissues; after apparently complete removal recurs, and, whether removed or not, secondary growths are common in the nearest lymphatic glands or in distant parts, or in both.

Though the patient is often in excellent health at the appearance of the tumor, he sooner or later wastes, loses strength rapidly, and becomes very anæmic; **cachexia** is produced. This is due to many causes—*e. g.* to removal from normal tissues of nutriment required for the active growth of the tumor-cells; perhaps to the metabolism of the latter, pouring abnormal excreta into the blood; to pain and anxiety; often to profuse discharge and septic absorption consequent upon ulceration; occasionally to actual interference with the ingestion and absorption of food. The more rapidly and the more completely a tumor produces these results, the greater its malignancy. Even growths of the same class vary much in these respects, and different classes do so still more. Though in a high degree characteristic of cancers, the purely clinical term "malignant" must be distinguished from the pathological term "cancerous," which implies a specific structure in the growth it refers to. Sarcomata are often quite as malignant as cancers.

RECURRENCE AND GENERALIZATION.—A tumor may recur *locally* after removal, and after or before removal growths similar to the primary tumor may form in the nearest **lymphatic glands** or in more **distant tissues** or **organs.** In the highest degrees of malignancy all these occur. Each of these must be considered separately.

Reproduction of the Tumor in Adjacent Structures.—This recurrence *in loco* after removal is usually the earliest, and is the slightest, evidence of malignancy. It is due to some of the tumor-cells having been left behind, and is therefore much more likely to occur in those growths which infiltrate the surrounding tissues and really extend beyond their *apparent* limits than in those which do not. The cells left behind continue to grow and recurrence occurs. Cells may be carried to some little distance from the primary growth by lymph- or blood-currents, and, becoming impacted, form secondary nodules around the original tumor. In some tumors local recurrence occurs many times, and often kills the patient without affection of glands or generalization (p. 162).

Reproduction of the Tumor in the Nearest Lymphatic Glands.—This is owing to the entry into and transmission by the lymph-stream of cells from the malignant growth, which become arrested in the nearest lymphatic glands and there develop into secondary tumors. These are in all cases of the same nature as the

primary tumor. When the lymphatic glands have themselves developed into secondary growths, they in their turn constitute new centres of infection, and may thus infect more distant glands or the immediately adjacent tissues. When the lymph-sinuses of a gland are so blocked by new growth that lymph cannot pass, a regurgitant flow is the natural result, and the lymph, bearing tumor-cells, has to pass through abnormal vessels and glands. In this way we can account for affection, say, of the abdominal glands by tumor of the lung, and for the numerous nodules in the skin which sometimes occur widely all around atrophic scirrhus of the mamma. A distant lymphatic gland may be infected by embolism of its artery. The tendency to reproduction in the lymphatic glands varies very much in the different varieties of malignant growths, being, for example, very marked in the carcinomata, whereas in the sarcomata it is less frequent. The reasons for these differences will be seen in the subsequent chapters (pp. 159, 182).

Reproduction of the Tumor in Distant Tissues. — This is usually the terminal process in the history of malignant growths. The reproduction of the malignant growth in distant tissues is, in the great majority of cases, owing to the entry of some of its elements into the blood-stream. The secondary tumors are therefore the result of embolism of tumor-cells; and the points at which the cell-masses may be arrested are stated in the chapter on Embolism (p. 226.) As in the lymphatic glands, they are in all cases of the same nature as the primary one, although they are often softer, more vascular, more active in growth, and may be larger. They may constitute secondary centres of infection, and in the same way cause tertiary growths in parts beyond.

Although the general dissemination of a malignant growth is thus in most cases owing to the transmission of its elements by the blood-stream, this is not the only way in which it may be brought about. Exceptional cases have been described in which the elements of a tumor have been distributed and have caused secondary growths in other ways, as by passing down the trachea, travelling between the layers of the peritoneum, or from the kidneys down the ureters to the bladder, etc.

Lastly, it must be borne in mind that growths may be secondary to each other only *in time*, being entirely independent of each other and originating from different primary foci.

We have spoken of generalization and lymphatic infection as cer-

tainly due to carriage of tumor-cells from the primary growth. The similarity in structure and the time-relation of primary and secondary growths, their demonstrable connection by vascular channels, and the fact that the secondary growths often occur in tissues in which primary tumors of their structure never occur, prove the origin of the secondary from the primary tumor. Some authorities think that carriage of the juice, and not of the cells, of the primary tumor is the cause of the secondary nodules. But the localized action, the distribution of secondary growths in the next capillary area, and the possibility of explaining exceptions to this rule; the occasional finding of tumor-cells in the blood, and more often impacted in vessels as emboli; the frequent demonstration of tumor growing into veins and lymphatics, both macroscopic and microscopic, so that cells may easily be swept off by, or migrate into, the stream; and the fact that secondary growths have never been found in cartilage or cornea which are permeable to fluids,—show that the cells rather than juice are the cause of secondary growths. Two views are held as to how they produce this effect:

1st. It is said that the cells impacted at a certain spot so influence the vessel-wall and surrounding tissues that their cells multiply and produce a structure like that of the infecting particle. The objection has already been stated to this spermatic influence, which would require us to believe that liver-cells, for example, may by their multiplication produce not only epithelial cells like those of scirrhus, columnar or squamous epithelioma, but connective-tissue cells of all kinds.

2d. The cells of the secondary nodule are believed to be the products of the multiplication of the cells of the tumor-embolus. The question thus arises: Can a bit of tumor thus cut off from its base grow? Artificial embolism of portions of fresh periosteum has been produced by Cohnheim and Maas, with the result that they grew and produced cartilage and then bone; but after the fifth week all trace of them had disappeared. In fact, they went through the same course as do pieces of normal tissue or of tumor which are placed in the subcutaneous tissue. We see, therefore, that they can grow, but something in the healthy tissues prevents their attaining any size. On the other hand, a piece of bone or other tissue, placed where it should normally exist, does not thus disappear, as the transplantation-experiments above quoted show.

THE CAUSES OF MALIGNANCY.—Why do some tumors invade adjacent tissues and generalize, whilst others do not, even though they grow as rapidly or more so than those which do? Hitherto difference in structure has been held to explain the matter. The more purely cellular the tumor, the richer it is in blood-vessels; and the less developed their coats, the more rapid its spread and the earlier and more certain its generalization.

But occasionally we find that a tumor which has run a simple course, and which does not recur after removal, has a structure necessitating its being placed among the sarcomata. Epulides, central sarcomata of bones, some sarcomata of the ovary and fasciæ, may grow to a large size without invading other tissues or generalizing. On the other hand, examples of the generalization of many simple tumors have been frequently recorded—*e. g.* chondroma, myxolipoma, even fibroma; also adenomata of the ovary and thyroid. It is true that connective-tissue growths do generally contain a preponderance of round cells before they generalize; but in some cases the structure of the secondary growths is that of the primary, and is such as is usually seen in specimens which show no malignancy. Cohnheim thinks, therefore, that the essential factor in "malignancy" is not a certain structure on the part of the tumor; but rather some change in the surrounding tissues which renders them unable to resist invasion. For from the way in which physiological tissues lie side by side, never invading each other's precincts, though one or both may be growing actively, it is evident that each tissue possesses a power which opposes infiltration by any other tissue; this power Cohnheim calls "**physiological resistance.**" Its existence is further shown by the experiments of Cohnheim and Maas alluded to above; which prove that bits of malignant growths or normal tissues transplanted into the tissues of a normal animal, may become vascularized and grow, but that they will shortly after disappear—the healthy tissues get the upper hand. To permit the infiltration of one tissue by the elements of another the physiological resistance of the former must be reduced. This may be effected by—(1) **Inflammation,** and therefore by injury: in chronic inflammation of epithelium-covered membranes (lupus, chronic glossitis, cirrhosis of liver, interstitial pneumonia, etc.) masses of epithelium are found in the infiltrated connective tissue (Friedländer). (2) **Age:** Thiersch showed that connective tissues atrophy after mid-life from diminished vital activity; probably diminished physiological resistance accompanies this, and thus the more active surface epithelium is

enabled to invade the sublying cutis. This he regarded as essential to the growth of an epithelioma. (3) **Heredity**: hereditary weakness on the part of the tissue surrounding a tumor-germ must be assumed in young people in whom neither injury nor age can be regarded as a cause of diminished physiological resistance. But even if no tumor can infiltrate in the absence of this change in the adjacent tissues, the structure of the growth probably has a marked influence upon its malignancy. Tumors which have great power of growth, whose cells are loosely held together, whose blood-vessels are numerous and thin-walled, and whose cells actually lie in lymph-spaces, must generalize more readily, when this is possible, than tumors in which opposite conditions obtain.

ETIOLOGY.—Nothing is really known on this point. We have to account for the presence in some tissue of cells which have an *ability to grow* more or less in excess of that possessed by the normal cells of that tissue. Increased *food-supply* will of course be required, but this is of secondary importance; as also are the surrounding physical conditions, which may be favorable or unfavorable.

At first, all tumors appear to be local, and **local causes** have consequently been sought. A causal relation seems in some cases to exist between **injury** or **irritation** and the formation of a tumor. But we know that the effects of these influences on normal tissues are inflammation and hyperplasia, and that they produce these effects even in those who are the subjects of tumors. Further, a history of injury cannot be obtained in 15 per cent. of the cases; and the injuries followed by tumors must constitute a very small proportion of the total number of injuries. Still, it is probable that injury, by producing hyperæmia and inflammation, may bring extra food to cells ready to grow, and may diminish the physiological resistance of the tissues round them. Irritation certainly seems to have a powerful effect in certain epitheliomata—as of the scrotum in sweeps, of old scars, and in rodent ulcers—but for the vast majority of cases no local cause can be found.

The cachexia produced by malignant growths, their very frequent recurrence, their multiplicity, and their hereditariness—all pointing to a deep affection of the whole organism, as it was thought—gave rise to the belief that they were of **constitutional** origin. This is a bad term, for it may mean *general*, and refer to the constitution of the whole organism, or it may refer to the constitution of certain

cells, and have a *local* significance. We shall therefore use the word *general.* Now, we already know how to explain cachexia, local recurrence, and multiplicity as results of a growth of the tumor, which was produced by multiplication of a few abnormal cells—*i. e.* by a local abnormality. There is therefore no need on these grounds to consider that the physiological processes of all the cells of the organism are abnormal and tend to produce cancer, or that removal of the primary growth would be useless, because continuance of the general abnormality would reproduce the disease elsewhere. Nor does heredity lead to this conclusion; for the whole of normal development is nothing but the transmission of local peculiarities; and, moreover, heredity is at least as marked in multiple simple growths—fibromata, warts, lipomata, osteomata—as it is in cancers. It is probable that *all* tumors are at first *local*, and that certain of them become malignant, as above explained; also that any inherited peculiarity which results in abnormal growth at a certain time affects only a few cells, or it may be many foci of cells, in one tissue, and not the organism at large. It is obvious, however, that neither the constitutional nor the local view makes any pretence at explaining how the abnormal ability to grow is acquired by the cells which give origin to the tumor. Cohnheim advanced an hypothesis which, if true, goes a step closer.

Theory of Embryonic Remains.—Thinking over the hypertrophies, the excessive formations (supernumerary digits and more marked examples of "monster by excess"), the teratomata, and other congenital tumors, all of which are admitted to be due to an embryonic cause, many of which are hereditary, and some of which do not appear for some years after birth, it occurred to Cohnheim that all tumors might be due to developmental faults. He supposed that more cells than are needed for a part are produced; the surplus remain in an embryonic state in one part or scattered over a whole tissue. The causes of this error, and the reason why the cells do not develop like their *confrères* and simply enlarge the part, are not known. We know little of such conditions of "resting" embryonic cells, perhaps because of their small size and resemblance to leucocytes. Small nævoid spots may enlarge greatly after birth; congenital moles which have the structure of alveolar sarcomata may later on become malignant, and islets of cartilage from which tumors may start have been shown by Virchow to occur in the shafts of long bones. Perhaps these may be regarded as embryonic remains.

Assuming that such embryonic foci may remain among adult tis-

sues, Cohnheim found that his view accorded well with facts observed. There would be no difficulty about the reversion of adult cells to the embryonic type; they would start with their full developmental force. Reasons for believing in the undeveloped nature of the rudiment are—that power of growth is at its greatest in the cells of the embryo, as is shown by the fact that embryonic cartilage, transplanted to the anterior chamber of the eye, grows into a regular chondroma (Leopold), whilst adult cartilage is absorbed; that many tumors are obviously distinct from the part in which they lie—*e. g.* adenoma of the mamma is encapsuled, and its ducts do not open into those of the normal gland; and that tumors are not subject to that regulating mechanism which renders the metabolism of each tissue subservient to the good of the tissues generally.

A large proportion of all tumors occur at points at which the developmental processes are complicated, and where, therefore, errors are most likely to occur. This is shown by the frequency with which epithelioma affects the openings on the surface of the body; the œsophagus where crossed by the left bronchus (the food and air-passage were originally one here); the cardia, pylorus, and commencement of the pyloric portion of the stomach, where change of epithelium occurs; the line of union of the invaginated epiblast and the hind-gut in the rectum; the external os uteri, where Müller's ducts opened into the urogenital sinus. Adeno-myomata of the prostate occur at the same spot in the male. Smooth myomata occur almost exclusively in the uterus. The whole uterus is made up of foci of cells awaiting the stimulus of impregnation to great development. Atypical development of one focus may occur without the usual stimulus, and perhaps we should rather expect this when pregnancy has been absent or infrequent. Myomata are commonest in elderly sterile women. Adenomata of the mammæ may be similarly explained.

Heterologous tumors are always so placed that it is possible to see how, by developmental error, some cells which would naturally give rise to the heterologous tissue might have been included in the tumor-germ. Thus dermoids occur near where invaginations of epiblast are normal. Muscle may easily get into the Wolffian bodies from neighboring muscle-plates, and cartilage from the rudiments of vertebræ, etc.

Finally, from so atypical a rudiment an atypical result would be expected.

Against Cohnheim's view it may be said that nothing is really

known of such embryonic remains; that many of the points of complicated development which he mentions are also points of irritation—*e. g.* the narrowings of the alimentary canal; that many tumors of the gullet and rectum, for example, though *near* the points mentioned, are not *at* them; and that he is obliged to exclude from his class of tumors such cases as epithelioma of scars, of the scrotum in sweeps, of the arm in paraffin-workers, in which irritation plays so obvious a part.

The exciting effect of **increased blood-supply** is evident in many cases—*e. g.* enlargement of ovarian dermoids at puberty, of tumors of the breast, ovaries, and uterus in pregnancy. This may cause the multiplication of cells capable of growth, and may explain the apparent causation of tumors by injuries.

Parasitic Theory.—Malignant or infective growths—carcinoma and sarcoma—present so obvious a resemblance to certain infective diseases, such as tuberculosis, in their obscure origin, tendency to spread locally, and dissemination by lymph- and blood-paths, that, the parasitic nature of the latter having been demonstrated, the former are naturally suspected of having the same etiology. Some pathologists lean strongly to the view that these growths begin by the inoculation at some spot of a germ which excites the cells to rapid multiplication, and that spread takes place from this focus by conveyance of the germ along lymph- and blood-paths. In the somewhat unusual cases of a general outbreak of malignant growths it is assumed that the primary focus, in which the poison was received and multiplied, was not recognized, a parallel being established between them and cases of general tuberculosis in which no caseous mass is found.

The "constitutional theory" is resuscitated, but it is now made to correspond to the "tubercular diathesis," or predisposition of certain tissues to permit the growth of the bacillus tuberculosis. It is no longer supposed that all the tissues of a cancerous patient are tending to grow cancerously or throwing something into the blood which will out somewhere, but merely that certain tissues will permit the growth of the hypothetical malignant germ should it reach them. This "malignant predisposition" may be inherited or acquired; it may be so strong that nothing is required for the production of a malignant growth but the arrival of the germ at a predisposed spot; or the physiological resistance of the tissues may require still further depression by injury or privation before they will permit the multiplication of the germ in their midst, the effect of irritation and injury being similar in the instances of tubercular disease starting after bronchitis

or strain of a joint, and of cancer following irritation by soot or tar or a blow. Irritation is, upon this view, in the case of cancer held to depress the vitality of the epithelium, and to cause it to admit to its own substance a germ previously resisted; and the frequent origin of cancer mammæ at the menopause, when the breast epithelium is degenerating, is quoted in support. The analogy between cancer and tubercle may be traced into even finer details: thus both, when they affect the face (rodent ulcer and lupus), take an unusual course—slow ulceration without affecting glands or distant parts and without causing cachexia.

It is further suggested in favor of the germ-theory that absorption of products of bacterial decomposition would help to explain the cachexia, and might account for the fever which accompanies the growth of some tumors, especially lymphomata; and that both the alleged incompatibility, so to speak, of active tubercular and cancerous disease in the same subject, and the rare disappearance of a malignant growth after a fever, especially erysipelas, may be due to the triumph of one organism over the other in the struggle for existence.

The presence of specific parasites in any tumor-emboli would, it is said, explain the growth of secondary tumors without the aid of any special diminution of the physiological resistance of the tissues in which the embolus lodges.

Lastly, there is a small number of cases recorded in which cancer of one labium has caused cancer of the opposing surface; and Cripps mentions a case of cancer of the arm resulting from contact with an ulcerating scirrhus: these are regarded as proving inoculability.

This concludes the *a priori* case which has been made out for the parasitic origin of tumors. With regard to positive evidence in its favor, there is really none. Gussenbauer alleges that he has discovered the cause in certain minute highly refracting particles in and between the cancer-cells. Other observers have failed to find any parasite by means of the ordinary staining methods; also by means of cultivations. Shattock and Ballance record[1] the results of cultivations from a large number of tumors, malignant and simple, in which no antiseptic (that might kill any germ) was used: all, after the earliest, remained sterile. They conclude that if the parasite is a protophyte it must be of a very special kind, and incline to the view that it is probably a protozoon, which either exercises a "spermatic

[1] *Path. Soc. Trans.*, 1887, p. 412.

influence" or lives as a true parasite in the epithelial cell, or, by conjugating with an epithelial cell, confers upon it fresh life and power of multiplication. Inoculations of cancer-juice upon man and animals have failed, the latter repeatedly; but it is argued, with fairness, that predisposition may be required.

In spite of the resemblance between the modes of spreading and consequent morbid anatomy of the malignant growths and tubercle—which really goes for very little—and of the alluringness of the other arguments adduced in favor of the parasitic origin of malignant growths, probability seems to us to be rather against than in favor of it, at least as regards the true cancers. In the infective granulomata (*q. v.*) bacilli carried by the lymph- or blood-stream lodge, and excite an inflammation similar to that which they caused at the primary focus: the cells of the granuloma are chiefly leucocytes—not the progeny of cells from the primary focus—and the tendency of the cells of granulomata is to degenerate, not to multiply excessively. It has hitherto been believed that secondary sarcomatous growths were truly the progeny of the primary growth, formed by multiplication of cells carried from the primary focus; and the melanotic nature of the secondary growths in melano-sarcoma has generally been regarded as proof of it, there being no positive evidence of "spermatic influence" (p. 125). But, as sarcoma-tissue is indistinguishable from inflammatory tissue, and as our beliefs as to the origin of sarcoma-cells are based on inferences, and not upon direct observation, it is possible that we are mistaken as to the nature of some morbid sarcoma-like processes, and that we shall find them to be inflammatory and to depend upon an infective cause, like rhino-scleroma (*q. v.*). With regard to the epithelial multiplication which characterizes true cancer, however, there can be no such mistake: the immediate cause of cancer must induce this. The question then arises: Is it conceivable, in the face of the necessarily deleterious action upon their host of all parasites, that this cause can be a parasite?

Reviewing the whole question, it is obvious that we have only more or less probable surmises before us. With regard to simple tumors, Cohnheim's theory of embryonic remains, which brings them into relation with "monsters by excess," seems to be the most likely. As to true cancers, the view that the physiological resistance of the connective tissue is reduced until epithelium, having, perhaps, only its normal tendency to grow, can invade it, appears to accord best with known facts: unusually rapid multiplication of epithelium would then

naturally result from increased food-supply. As to the etiology of the sarcomata, there is even less ground for surmise.

CLASSIFICATION.—Tumors having the most obviously similar structure vary much in their clinical history, whilst others of radically different structure have very similar physical signs and courses. Consequently a clinical classification cannot be constructed, and we are obliged to fall back upon a histological classification based upon the resemblance of every tumor to some normal tissue, adult or embryonic.

For convenience' sake all cysts will be grouped together and remarks on them made at the end of Tumors, though the great majority of cysts are not tumors.

Classification of Tumors.

Mesoblast.

I.—*Type of Fully-developed Connective Tissues.*

Type of fibrous tissue	Fibroma.
" mucous "	Myxoma.
" adipose "	Lipoma.
" cartilage	Chondroma.
" bone	Osteoma.
" lymphoid tissue	Lymphoma.

II.—*Type of Embryonic Connective Tissue.*

The varieties of sarcoma.

III.—*Type of Higher Tissues.*

Type of muscle	Myoma.
" nerve	Neuroma (see note on p. 180).
" blood-vessels	Angioma.
" lymphatic vessels	Lymphangioma.

IV.—*Type of Epithelial Tissues.*

Epiblast and Hypoblast.	Papillæ of skin or mucous membrane	Papilloma.
	Glands	Adenoma. Carcinoma.

V.—*Teratomata, or Congenital Mixed Tumors.*

CHAPTER XIII.

THE FIBROMATA.

DEFINITION.—The fibromata, fibro-cellular, or connective-tissue tumors are tumors consisting of fibrous tissue.

HISTOLOGY.—The fibres, which constitute the chief part of the growth, are loosely or densely packed according to the variety, and are arranged either without definite plan or in intercrossing bundles of various sizes or in whorls around the blood-vessels (Fig. 33). Yel-

FIG. 33.

Fibrous Tumor from the Skin: Near the cut blood-vessel, V, are seen some cells; also fibres cut transversely. × 200, and reduced 2.

low elastic fibres are very rarely met with. The cells, like those of normal fibrous tissue, are generally few in number, and are usually most abundant around the vessels. They are minute, spindle-shaped, fusiform, or stellate bodies, the latter having processes of varying length which communicate with similar processes from neighboring cells. They are often so small and indistinct in the fresh specimen as to become visible only after the addition of dilute acetic acid. These cells in size and number vary with the rapidity and age of growth—the slower and older the growth, the denser the tissue, the flatter and less numerous the cells.

The fibromata usually contain but few blood-vessels. In the softer growths, however, these are often more numerous. Dilated veins sometimes form a cavernous network, the walls of which are firmly

united to the tissue of the tumor, so that when divided or ruptured they are unable to retract or collapse, and profuse hemorrhage may ensue.

SECONDARY CHANGES.—Partial **mucoid softening** and **calcification** are the most common; ossification occurs in fibromata springing from bone. **Ulceration** also sometimes occurs in those growths which are situated in the skin and submucous tissues.

VARIETIES.—Fibrous tumors present two varieties, the **soft** and **hard**, corresponding to, and usually originating from, the loose and dense varieties of ordinary connective tissue respectively.

1. **Soft Fibromata.**—These consist of the looser and less dense form of fibrous tissue. They are met with as diffused growths in the subcutaneous and submucous tissue. In the former situation they often form large pedunculated and non-encapsuled tumors, which are commonly known as **wens**. These are sometimes multiple. A similar growth of subcutaneous tissue is met with in **molluscum fibrosum**. In this disease the large masses which hang down from the thighs, buttocks, and other situations consist simply of loose fibrous tissue. They often contain numerous large blood-vessels, so that their removal may lead to severe hemorrhage.

In addition to these diffused growths, more circumscribed and **encapsuled** fibrous tumors of the soft variety are occasionally met with growing from the scalp, scrotum, labium, intermuscular septa, and other situations.

2. **Firm Fibromata.**—These are composed of dense fibrous tissue, like that in tendons. They are firm, hard, encapsuled tumors, presenting on section a grayish-white, glistening, fibrous appearance. These tumors often occur in connection with bone, especially with the upper and lower jaws, originating either in the centre of the bone or from the periosteum. Growing from the periosteum of the alveolus, they constitute simple fibrous **epulis**. They are met with also in the nose, where they form one variety of **nasal polypus**, and in the naso-pharynx, springing from the front of the spine or from the base of the skull. In these firm fibrous growths the veins may form cavernous spaces.

Another variety of firm fibrous tumor grows in connection with nerves, and is often described as **neuroma**. True neuromata, however—*i. e.* new formations of nerve-tissue—are among the rarest

forms of new formations. These fibrous growths most frequently occur in connection with the superficial nerves. They grow from the neurilemma, and as they increase in size the nerve-fibres become expanded over them. They are very firm rounded tumors, and are frequently multiple and hereditary.

Some old tumors of the uterus are almost or quite pure fibromata; but the so-called uterine "fibroids" are in most cases overgrowths of the involuntary muscular tissue of the organ. (See "Myomata.")

SEATS.—The fibromata originate **from connective tissue,** from the cutis or subcutaneous tissue, from submucous or subserous tissue, from fascia, the periosteum, the neurilemma, or the connective tissue of organs.

CLINICAL CHARACTERS.—The fibromata are perfectly innocent: they grow slowly and do not recur after removal.

PSAMMOMA.

The most characteristic feature of this rare growth is that it consists largely of calcareous particles. These are contained in the concentric bodies already described as the corpora amylacea, where they give rise to the so-called "brain-sand;" hence the name of the growth. The calcified corpora amylacea are held together by a varying quantity of loose fibrous or highly cellular or mucous tissue containing vessels.

Psammoma grows from the pineal gland, the membranes of the brain, or the choroid plexus. In the latter situation it often contain numerous cysts. It is of no pathological importance except when of sufficiently large size to produce symptoms from pressure.

CHAPTER XIV.

THE MYXOMATA.

DEFINITION.—The myxomata consist of mucous tissue—*i. e.* connective tissue of which the intercellular substance is translucent, homogeneous, and jelly-like, contains much fluid, and yields mucin.

Physiologically, this tissue is met with the vitreous body of the eye, in which the cells are roundish and isolated; in the umbilical cord, in which the cells are fusiform or stellate and give off fine anastomosing prolongations. All embryonic connective tissue (p. 80) possesses an intercellular substance containing much mucin, especially that which subsequently becomes adipose. New formations may undergo mucoid degeneration, and thus closely resemble in their physical and chemical characters the myxomata; but a myxoma consists of mucous tissue from the first. The myxomata are thus very closely allied to the sarcomata, and by many are included in the same class of new formations. An œdematous fibroma or lipoma closely resembles a myxoma or myxo-lipoma: Köster believes that they are identical.

FIG. 34.

Myxoma: from the arm, showing the characteristic branched anastomosing cells, a few leucocytes, and one or two spindle-cells. × 200.

HISTOLOGY.—The majority of the cells are angular and stellate, with long anastomosing prolongations; others are isolated, and fusiform, oval, or spherical in shape (Fig. 34). Their contour is very indistinct, owing to the refractory nature of the intercellular substance. The latter is very abundant, perfectly homogeneous, soft, gelatinous, viscid, and yields large quantities of mucin: in it are a varying number of amœboid cells. Blood-vessels are not numerous, and are readily visible and easily isolated. A few elastic fibres are sometimes seen between the cells.

SECONDARY CHANGES.—Of these the most common is rupture of the capillaries, **hemorrhage**, and the formation of **blood-cysts**; this, however, is less frequent than in the sarcomata. The cells themselves may undergo **mucoid** or **fatty degeneration**, and thus be destroyed: this is usually accompanied by liquefaction of the intercellular substance. The growth may **inflame**, ulcerate, and necrose.

VARIETIES.—The varieties of myxoma depend principally upon

its combination with other growths; a pure myxoma is very unusual. The most common is a combination with lipoma. Combinations with sarcoma, fibroma, chondroma, and adenoma are also met with.

PHYSICAL CHARACTERS, ETC.—The myxomata are of a peculiar soft gelatiniform consistence and of a pale grayish or reddish-white color. Their cut surface yields a tenacious mucilaginous liquid in which may be seen the cellular elements of the growth. They are usually separated from the surrounding structures by a very thin fibrous capsule, fine prolongations from which divide the growth into lobules of various sizes. In exceptional cases they may increase by the continuous invasion of surrounding tissues.

SEATS.—Myxomata grow from **connective tissue**, and are most common in subcutaneous and subserous fat, submucous and intermuscular tissue. They grow also from periosteum and medulla of bone, from the connective tissue of organs (especially the breast), and from the perineurium of nerves, forming one variety of "neuroma." They may grow also from the placenta, constituting the "uterine hydatids."

When situate in superficial parts they may become pedunculated, constituting in the submucous tissue of the nose one form of nasal polypus. In the skin they are often papillary

CLINICAL CHARACTERS.—Myxomata occur chiefly after mid-life, and are for the most part benign. Their growth is usually slow, but they may attain an enormous size. If completely removed they rarely recur. Sometimes, however, they recur locally after removal, but they probably never reproduce themselves in internal organs. In speaking of their malignancy their occasional association with sarcoma must be borne in mind.

CHAPTER XV.

THE LIPOMATA.

DEFINITION.—A **lipoma** or fatty tumor is a localized and circumscribed formation of fat.

HISTOLOGY.—The lipomata resemble in their structure adipose

FIG. 35.

Lipoma: Some of the cells contain crystallized fatty acids. × 200.

tissue (Fig. 35). They consist of cells containing fat and a variable quantity of common connective tissue. The cells are like those of adipose tissue, though usually somewhat larger. The nucleus and protoplasm are so compressed against the cell-wall by the fluid contents that they are readily visible only when the cell is atrophied and contains less fat. (See Fig. 4.) Connective tissue varies much in amount, unites the cells in masses or lobules which are larger than normal, and forms in most cases around the tumor a thin capsule more firmly adherent to surrounding parts than to the tumor; so the latter in most cases "shells out" easily. Blood-vessels are distributed in the fibrous septa. Mucous tissue is often associated with the fatty (myxo-lipoma).

SECONDARY CHANGES.—Secondary changes in the lipomata are not common; their fibrous septa may, however, become **calcified**, or even **ossified**. Softening may occur also from a **mucoid** change. **Inflammation** is rare, but when large and situated in the subcutaneous tissue the skin over them may become adherent, and ulceration and necrosis of the tumor occur.

VARIETIES.—The chief are the **fibro-lipoma**, in which the fibrous tissue is excessive, and the **myxo-lipoma**, or combination of mucous with fatty tissue. (For **lipo-sarcoma**, see p. 158.)

PHYSICAL CHARACTERS, ETC.—The lipomata are more or less lobulated, and usually surrounded by a fibrous capsule. They move freely over the deep fascia when subcutaneous, but often the attempt to raise the skin from them causes it to dimple. On section they present the ordinary appearance of adipose tissue; more or less dense fibrous septa are seen between the lobules. Their consistence and adhesion to the capsule vary with the amount of fibrous tissue which they contain. In their growth they occasionally become pedunculated.

SEATS.—Lipomata grow from **connective tissue** and are in dis-

tribution almost coextensive with that of adipose and connective tissue. They occur most frequently in the subcutaneous tissue of the trunk, especially of the back and abdominal wall; sometimes in intermuscular septa, subsynovial and subserous tissues; and occasionally also in the submucous tissue of the stomach and intestines, and even in internal organs where there is normally no fat.

CLINICAL CHARACTERS.—The lipomata are quite innocent; they grow slowly, but may attain a huge size; they are usually single, but are not infrequently multiple and hereditary. They sometimes change their position considerably, gliding under the influence of gravity.

CHAPTER XVI.

THE CHONDROMATA.

DEFINITION.—The chondromata are tumors consisting of cartilage.

HISTOLOGY.—Like cartilage, they consist of cells and of an intercelluar substance, which present all the variations observed in the normal tissue. The intercellular substance may be hyaline, faintly or distinctly fibrous, or mucoid. When fibrous, the fibres may be arranged like those of fibro-cartilage or more or less concentrically around the cells, as in the recticular cartilages of the ear and larynx (Fig. 36). When hyaline or mucoid, it is sometimes quite soft in con-

FIG. 36.

Fibrous Chondroma. × 200.

FIG. 37.

Hyaline Chondroma. × 200.

sistence. The cells may be very numerous or few in proportion to the matrix. In the hyaline forms they are usually large and round or

oval (Fig. 37); in the fibrous forms they are often smaller and even somewhat spindle-shaped, more resembling those of connective tissue; and in the rarer mucoid forms they are more commonly stellate and branched, like the transitional cells at the edge of articular cartilages where the synovial membrane ends. They are either single or arranged in groups, and are usually surrounded by a capsule, as in normal cartilage, although this is often very indistinct. They enclose one or more nuclei and slightly granular contents; sometimes a cell-wall cannot be distinguished.

SECONDARY CHANGES.—Calcification is the most common, because frequent in the commonest chondromata—those of the phalanges and metacarpals of the hands. It spreads from many centres, commencing in the capsules, and then involving the intercellular substance. **Ossification** also occurs, especially in the chondromata which grow near the junctions of the epiphyses and shafts of long bones; these ossify as they grow and form the pedunculated exostosis. So also does the common subungual exostosis of the great toe, which is generally an ossifying fibroma, chondroma, or fibro-chondroma. **Fatty degeneration** and **mucoid softening** are common changes, and may lead to the formation of large softened masses which present the appearance of cysts. In rare cases the skin covering the tumor ulcerates and a fungating mass protrudes.

VARIETIES.—The varieties of chondroma depend upon the nature of the intercellular substance, and are **hyaline, fibrous,** and **mucoid**; these are often variably combined in the same tumor. As a rule, those originating from the medulla of bone are of the hyaline and mucoid class, whilst those originating from connective tissue in other situations are more frequently fibrous. The rapidly-growing fibrous forms approach very closely to the sarcomata (**chondro-sarcoma**), the mucoid forms to the myxomata (**myxo-chondroma**); and these two kinds of growth are often associated in the same tumor. Chondromata are rarely homologous in the strict sense (p. 126).

A variety of chondroma has been described under the name of **osteo-chondroma,** which in structure more closely resembles bone than cartilage. It consists of a tissue similar to that met with between the periosteum and bone in rickets, which, from its resemblance to osseous, has been called **osteoid** tissue. This requires only calcifying to become true bone. Like bone, it is made up of trabeculæ and

medullary spaces; but the trabeculæ, instead of bone-corpuscles and lamellæ, consist of small angular cells without a capsule, situated in an obscurely fibrillated matrix which in part is calcified. The medullary spaces contain a fibrous stroma and many blood-vessels. The osteo-chondromata, although consisting mainly of this osteoid tissue, contain also a small proportion of cartilage. They originate beneath the periosteum, their common seat being the ends of the long bones. Their growth is very rapid, and they often attain an enormous size. They are much more freely supplied with blood-vessels than the ordinary chondromata, and hence they are much less frequently the seats of retrogressive changes. They are especially prone to become ossified and converted into true bone.

PHYSICAL CHARACTERS, ETC.—The more slowly growing chondromata are hard or slightly elastic tumors, smooth or lobulated, and seldom exceeding the size of an orange. They are encapsuled, and consist of a single tumor or of several smaller masses held together by fibrous tissue in which the few blood-vessels run, and present upon section the appearance and consistence of hyaline or fibro-cartilage, frequently altered by one or other of the secondary changes above mentioned. The appearance of a fibroma may be presented, the cartilage-cells being only microscopically recognizable.

The more rapidly-growing forms, such as often start from the pelvic bones or ribs—myxo-chondromata, osteo-chondromata, and chondro-sarcomata—are much larger, softer, and more vascular, and never present the appearance of pure cartilage: only islets at most will be distinct in the soft grayish tissue, which is not separated by any capsule from the adjacent tissues.

SEATS.—Chondromata spring most frequently from common **connective tissue** and **bone**, *very rarely* from cartilage. About three-fourths of them start in connection with bones, growing either centrally or subperiosteally. Their favorite seats are—the bones of the fingers and toes, the lower end of the femur and the upper of the humerus and tibia; much less often the ribs and the hip-bone are attacked. Virchow has shown that islands of cartilage not uncommonly remain in the shafts of bones, and has rendered it probable that many chondromata spring from them (p. 133). They generally begin before the ossification of the epiphyses, whilst the bone is actively growing and vascular.

Most of the remaining fourth occur, in combination with other tissues, as "mixed tumors" of the **parotid** and **testicle**. Cohnheim suggests as the source of cartilage in the parotid an aberrant bit of the rudiment of the jaw; Virchow, a piece of the pinna. In the testis a portion of the rudiment of a vertebra may have been included. The intermuscular septa, the subcutaneous tissue of the breast, and the lungs are occasional seats.

Lastly, cartilaginous growths may originate from **cartilage** itself (**ecchondroses**). These are sometimes seen on the surface of the articular cartilages, in the larynx and trachea, and on the costal and intervertebral cartilages. They are simply local overgrowths of hyaline cartilage.

CLINICAL CHARACTERS.—The chondromata must for the most part be regarded as innocent growths. They are usually single, except when occurring on the fingers and toes, in which situation they are more frequently multiple. The central growths of the phalanges and metacarpals occur in children or before ossification is complete: the subperiosteal graver forms are commoner later.

The softer forms, especially those starting from bone and glands, occasionally exhibit more or less malignancy, tending to recur locally, and, rarely, infecting the lungs and even other parts.

CHAPTER XVII.

THE OSTEOMATA.

DEFINITION.—The osteomata are tumors consisting of bone, either compact or cancellous.

The osteomata being the result of the ossification of *newly-formed connective tissue*, which is *not* a product of inflammation, must be separated from simple ossification of normally existing tissues—such as rib, laryngeal, or bronchial cartilages, insertions of muscles (riders' bone in adductor longus and the like), and membranes of the brain; and also from ossifications of inflammatory tissue, such as nodes or general thickenings of bones, the sharp stalactitic processes which may grow round a carious joint or surface of bone, and the smooth round prominences which form round a joint in rheumatoid arthritis. They

must be distinguished also from calcareous deposits in which there is no bone formed. (See "Calcareous Degeneration.")

VARIETIES: THEIR HISTOLOGY and PHYSICAL APPEARANCES.—1. **Homologous osteomata,** subdivided into **exostoses** and **enostoses** according as they project from the surface or into the medullary canal of a bone; 2. **Heterologous osteomata.**

1. **Homologous osteomata**: *a*. **Exostoses** are divided, according to the density of the bone of which they consist, into two kinds—(*α*) the *compact*, *ivory*, or *eburnated*; and (*β*) the *cancellous* or *spongy*.

(*α*) The **ivory exostosis** grows from periosteum. It occurs most frequently on the external and internal surfaces of the skull: the orbit is an especially favorite seat. It is met with also on the scapula, pelvis, and on the upper and lower jaws. In the last-named situation it may grow from the dental periosteum.

Such growths are smooth, low, rounded, and wide-based, covered by the periosteum, continuous with that of the old bone, from which they grow. On section they are throughout of ivory-like density, and they are usually well defined from the adjacent tissue. Microscopically, the lamellæ are arranged concentrically and parallel to the surface of the tumor; cancellous tissue is absent, and Haversian canals are few and narrow. Some specimens are less dense, the Haversian canals being as numerous as in ordinary compact bone, but less regularly arranged.

(*β*) The **spongy** or **cauliflower exostosis** is really an ossifying chondroma: it grows from cartilage, usually near the line of junction of an epiphysis of a long bone with the shaft—especially at the lower end of the femur and at the upper of the tibia and humerus. Its outline is less regular than that of the ivory growths; but it is prominent and pedunculated generally, and covered by a cap of cartilage so long as it is growing. When this ossifies, growth ceases. On section the mass consists of spongy bone directly continuous with the cancellous tissue of the bone whence it springs, and surrounded by a thin layer of compact bone. The medullary spaces may contain embryonic, fibrous, or fatty tissue.

(*b*) The **enostosis** is a dense growth springing from the medulla, and is very rare.

2. **Heterologous osteomata** are very rare as primary growths. They have been described as occurring in the subcutaneous tissue, but Malherbe has shown reason for believing that such growths are

really sebaceous adenomata of which the stroma is ossified. Bony tumors have very rarely been found in the brain and cerebellum. Parts of fibromata, lipomata, and chondromata may ossify. The secondary growths of ossifying sarcomata in connection with bone often ossify.

SECONDARY CHANGES.—Osteomata may **inflame,** become carious, or necrose. The latter is most likely to occur in ivory exostoses, causing their separation and cure.

SEATS.—Osteomata are much commoner in connection with **bone** (homologous) than elsewhere, growing from the periosteum, medulla, or persistent islands of cartilage; but **connective-tissue tumors,** apart from bone (heterologous), may ossify.

CLINICAL CHARACTERS.—The osteomata are perfectly innocent tumors. Their growth is very slow. They rarely attain a large size. They are often hereditary and multiple, in which case they usually occur in early life. Osseous growths which exhibit malignant characters are chondromata or sarcomata which have undergone partial ossification. From these true osteomata must be carefully distinguished. (See "Osteoid Sarcoma.")

CHAPTER XVIII.

THE LYMPHOMATA.

DEFINITION.—The lymphomata are new formations consisting of lymphoid, or, as it is sometimes called, adenoid tissue (His).

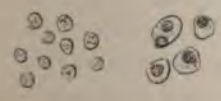
Lymphoid tissue is now known to have a much more general distribution than was formerly supposed. It not only constitutes the follicles of the lymphatic glands and the Malpighian corpuscles of the spleen, but also Peyer's glands and the solitary glands of the intestines, the follicles of the pharynx and tonsils, the thymus gland, and the trachoma glands of the conjunctiva. Recently it has been found to exist also in many other situations, as around the blood-vessels of the pia mater and of other parts, in the neighborhood of the smallest bronchi, in the pleura immediately beneath its endothelium, in the

peritoneum, in the mucous membrane of the alimentary canal, and in the medulla of bone.

HISTOLOGY.—Wherever it exists, the same general structure, that of the follicle of a lymphatic gland, may be taken as the type not only of physiological lymphoid tissue, but also of that of pathological growths.

This tissue consists of a delicate reticulum, within the meshes of which are numerous lymph-corpuscles. The reticulum is a close network of very fine fibrils, the meshes of which are only sufficiently large to enclose a few, or even a single corpuscle, in each. The fibrils usually present a more or less homogeneous appearance, and nuclei are sometimes to be distinguished at the angles of the network. The lymph-corpuscles, which constitute the greater part of the tissue, can in most cases be readily removed from the meshes of the reticulum by the agitation of thin sections in water. They are identical in their characters with the white cells of the blood. As usually seen after death, they are spheroidal, pale, semi-transparent bodies, varying considerably in size, and presenting slight differences in structure. Some are granular, and appear to possess no nucleus; in others, a distinct, simple, or compound nucleus is visible, which is usually also granular; others, again, are much larger and contain two or even three nuclei (Fig. 38).

FIG. 38.



Cells from a Lymphatic Growth in the Liver: Those to the left are the ordinary lymph-corpuscles, which constitute the greater part of the growth. To the right are some of the larger elements. × 350.

FIG. 39.

Lymphoma: Section of a firm lymphoma of the mediastinum, showing a very thickened reticulum, within the meshes of which the lymphoid cells are grouped. × 200.

The histological and physical characters of the lymphomata, however, vary considerably, according to the rapidity of their development. In the rapidly-growing forms the proportion of cells is very great, and many of them are larger than those normally met with in

lymphatic glands, containing two, or even more, nuclei; they are of a grayish-white color and soft brain-like consistence—much like encephaloid cancer—and yield abundance of milky juice. They may reach a great size. The more slowly-growing tumors, on the other hand, are less richly cellular, and the larger cell-forms are almost entirely wanting; the reticulum constitutes a more prominent part of the growth (Fig. 39), and, instead of being exceedingly delicate, is much coarser, and forms a network of broad homogeneous or slightly fibrillated bands. As the reticulum increases the lymph-corpuscles gradually diminish in number and become arranged in smaller groups within its meshes (Fig. 39). Such growths are much harder than the more rapidly-growing ones; they are sometimes exceedingly dense, and are rarely very large. These variations in the proportion of cells and stroma are precisely analogous to those met with in lymphatic glands as the result of acute and chronic inflammation (see "Inflammation of Lymphatic Structures"); but in many cases the relation between cells and stroma remains normal, as in hyperplasia.

SECONDARY CHANGES.—The lymphomata do not undergo marked retrograde changes. There is *little tendency* to fatty degeneration, caseation, or softening, such as occurs in scrofulous glands.

SEATS.—The lymphomata originate from lymphoid tissue, being apparently uniform overgrowths of pre-existing lymphatic structures—mainly of the lymphatic glands. They are therefore usually homologous. They may, however, be heterologous, either owing to the new tissue extending considerably beyond the confines of the old, or to its origin in situations where lymphoid tissue is not present normally. This latter condition obtains in Hodgkin's disease and in certain forms of lymphoma which are malignant.

In some cases of round-celled sarcoma, which may originate in any connective tissue, the matrix undergoes development into a network; the growths spread and generalize like ordinary sarcomata, and are called **lympho-sarcomata**. They may originate in lymphatic glands.

In considering the development of these growths it must be borne in mind that enlargements of lymphatic structures are most frequently of an inflammatory nature, being due to some injury; and histologically, as already indicated, there is but little difference between these inflammatory growths and lymphomatous tumors. The inflam-

matory growths, however, tend to subside, the tumors continuously to increase. Further, the development of the tumors may, like that of the inflammatory growths, be determined by some injury, the injury producing perhaps some inflammation and enlargement of the gland, but this, instead of subsiding, continues more or less rapidly to increase. (See "Etiology of Tumors.")

CLINICAL CHARACTERS.—Clinically, the lymphomata are, for the most part, perfectly innocent tumors. They originate most frequently in the lymphatic glands, the gland undergoing a continuous increase in size. Sometimes, as already stated, the enlargement of the glands appears in the first place to be of an inflammatory nature and to result from some irritation, but upon this being removed the glands, instead of subsiding, continue to increase. In most cases, however, no such source of irritation is discoverable. The glands which are especially prone to this disease are the cervical, the submaxillary, the axillary, the inguinal, the bronchial and mediastinal, and the abdominal glands. Usually only a single gland or a single group of glands is affected; sometimes, however, the growth is more general. As the glands enlarge they gradually unite, so that ultimately they may form very large lobulated tumors. When occurring in the mediastinum they may invade one or both lungs, and they constitute here the most common form of mediastinal tumor (so-called "thoracic cancer"). The lymphatic structures in the intestine may in the same way become enlarged, and project so as to form polypi.

The lymphomata occasionally, however, exhibit malignant properties. This is especially the case in those richly-cellular, soft, rapidly-growing forms which are sometimes met with. Such growths may rapidly infiltrate the surrounding structures, involve the neighboring lymphatic glands, and even infect distant parts. To these malignant forms the term **lymphadenoma** is sometimes applied. They correspond with Virchow's **lympho-sarcoma.**

In the condition known as "Hodgkin's disease" and in lukæmia lymphomatous growths are met with in various parts of the body.

HODGKIN'S DISEASE.

This disease is characterized by the enlargement of the lymphatic glands in various parts of the body, together with the development of lymphatic growths in internal organs, especially in the spleen;

by a diminution in the number of red corpuscles in the blood; and by progressive anæmia. The new growths are precisely similar, histologically, to lymphoma. The disease was described by Hodgkin, Bright, Wilks, and Trousseau, and is called, after the first named of these observers, "Hodgkin's disease;" Trousseau designated it "adénie;" it is also known as "anæmia lymphatica." It is allied to leukæmia, but differs essentially from it in this respect, that the new formation of lymphatic tissue is not associated with any notable increase in the number of the white corpuscles in the blood. (See "Leukæmia.")

The lymphatic glands are usually the earliest seats of the new growth. At first only a single group of glands may be enlarged; subsequently, however, the process becomes more general, and the glands throughout the whole body may be more or less involved. The groups of glands most frequently affected, in the order of their frequency, are the cervical, the axillary, the inguinal, the retro-peritoneal, the bronchial, the mediastinal, and the mesenteric. The new growth, which in the earlier stages is limited to the glands, gradually breaks through the capsules, so that the enlarged glands become confluent and form large lobulated masses. The growth may also extend still farther beyond the confines of the gland and invade and infiltrate the adjacent structures.

This new growth of lymphatic tissue, which commences in, and often extends beyond the confines of, the lymphatic glands, is ultimately followed by the formation of lymphatic growths in various internal organs, but more especially in the spleen. The spleen is affected in a large proportion of cases. Here the new growth originates in the Malpighian bodies, and so gives rise to disseminated nodules. These vary in size from minute points to masses as large as a hazelnut or walnut. They are usually more or less irregular in shape, of a grayish or yellowish-white color, firmer in consistence than the splenic tissue, and not encapsuled. In addition to these, wedge-shaped infarctions surrounded by a zone of hyperæmia are sometimes met with, similar to those which are often seen in leukæmia. The spleen itself is increased in size, although rarely very considerably so, and its capsule is usually thickened and often adherent to adjacent organs. In quite exceptional cases the spleen is not the seat of these disseminated growths, but is simply uniformly enlarged, like the leukæmic spleen.

The liver, kidneys, alimentary canal, medulla of bone, lungs, and

subcutaneous tissue may all become involved, the new growths occurring either as nodules of various sizes scattered through the organs, or in a more infiltrated form, like many of those met with in leukæmia.

Histologically, the new growths are precisely similar to the lymphomata, and like these present differences in the relative proportions of cells and stroma, the richly cellular forms being soft and pulpy, whilst those in which the stroma is more abundant are firmer and more fibrous in consistence. Retrogressive changes rarely occur.

With regard to the pathology of the disease, it is undoubtedly obscure. The development of the new growths cannot in most cases be regarded as the result of infection from a primary centre, as the process is, for the most part, confined to the lymphatic structures, and many and widely distant groups are often simultaneously involved. The disease thus appears to occupy a different pathological position to that of the malignant tumors. It is probable that there is some special weakness of the lymphatic structures generally which renders them prone to undergo these active developmental changes, the process being determined by some constitutional state or by some local injury of the glands. The progressive anæmia which accompanies, but does not precede, the gland affection is due to the progressive implication of the lymphatic structures and to the consequent interference with the formation of the blood-corpuscles.

Leuchæmia.

In leuchæmia, as in Hodgkin's disease, there is usually a development of lymphomatous tissue in various organs. The disease, however, is characterized by the large increase in the number of white corpuscles in the blood, and in the majority of cases by enlargement of the spleen. It is this alteration in the blood which gives leuchæmia its distinctive characters, hence its name. The disease will be considered subsequently when treating of "Diseases of the Blood."

The Lymphangiomata.

The lymphangiomata are tumors consisting of lymphatic vessels which are larger than normal, but it is doubtful what shares simple dilatation and new formation of lymphatic vessels take. The divisions are the same as those of angioma—simple and cavernous lymph-

angioma. A section of the latter would scarcely be distinguishable from one of cavernous nævus (see Fig. 50), except by the contents of the spaces. There is generally fat in the stroma.

Each kind may be congenital or acquired. Congenital dilatations are found in the tongue (makro-glossia), lip (makro-cheilia), and labium, causing hypertrophy of the parts; and also elsewhere in the skin.

Acquired dilatation is not rare in the skin, especially of the thigh and thorax, forming tumors sometimes as large as an orange in the subcutaneous tissue; dangerous loss of lymph may occur from rupture of a vessel. Fibroid thickening of the parts from which lymphatics pass to the tumor may occur.

CHAPTER XIX.

THE SARCOMATA.

DEFINITION.—The sarcomata are tumors consisting of connective tissue which throughout its growth more or less retains an embryonic type, in so far, at least, that cells predominate over intercellular substance. But in central parts the process of development leads not uncommonly to the formation of a more highly organized structure, such as fibrous tissue, cartilage, or bone—a mixed tumor resulting.

GENERAL HISTOLOGY.—All sarcomata consist of cells imbedded in more or less intercellular substance, which varies much in amount and character and bears the blood-vessels.

The **cells**, which usually constitute almost the whole of the growth, consist for the most part of masses of nucleated protoplasm, and rarely possess a limiting membrane. They vary much in size and form; and though in a tumor one form usually predominates, all may generally be found by searching teased preparations, which should always be employed to discover cell-forms (Cornil and Ranvier). Often the different forms are much mixed in the same growth. There are three principal varieties—**round**, **fusiform** or **spindle**, and **myeloid** cells. The round and spindle forms may be either small or large, and the multinucleated, irregular myeloid cells vary

much in size and in the number and size of the contained nuclei. One cell may have as many as thirty.

The **intercellular substance** exists usually in small quantity only, *intervening between all cells*, and somewhat *closely connected with them* as in ordinary connective tissue. These points are often relied upon to distinguish certain sarcomata from cancers, but they probably do not always hold good.

The stroma may be fluid and homogeneous, firmer and granular, more or less fibrous, chondrified, and ossified. On its amount and nature the consistence of the growth depends.

The **blood-vessels** are usually very numerous, and are either in direct contact with the cells or separated from them by a little fibrillated tissue. Their distribution is very irregular, and their walls are often formed by the cells of the tumor. Hence the ease with which early generalization can occur, and the frequency with which rupture and extravasation of blood take place. Lymphatics are not known.

An examination of the growing border usually shows a great excess of small round cells over all other forms; they extend along the connective tissue in all directions, between the essential elements of any muscles, glands, or other adjacent organs; and these elements become pale, atrophy, and disappear. In the invaded connective tissue many cell-forms are seen, which may possibly indicate multiplication of the fixed cells, but it is almost impossible to obtain any proof that they help to form the tumor.

In an ordinary examination of a sarcoma the growing edge should be avoided, on account of the predominance here of small round cells over the cells most characteristic of the tumor.

SECONDARY CHANGES.—The most important of these is **fatty degeneration.** This always occurs to a greater or less extent in the older portions of the growth, causing softening or the production of cyst-like cavities. It is frequently associated with rupture of the blood-vessels and **hemorrhage**; the latter may give rise to the formation of sanguineous cysts. (See "Blood-Cysts," p. 168.) **Calcification** (Fig. 46), **ossification** (Fig. 47), and **mucoid degeneration** are less common. The occurrence of calcification, ossification, and pigmentation is influenced by the predisposition of the matrix from which the growth is produced; thus, calcification and ossification are more prone to occur in tumors originating in connec-

tion with bone—pigmentation in those originating from the cutis or eyeball.

VARIETIES.—Though all sarcomata possess the same general characters, they present histological and clinical differences which serve as bases for their classification.

First, we get groups characterized by the *form* of the *majority* of the *cells*, **round, spindle,** or **myeloid**; giant-cells can never be said to predominate, but they are frequently so numerous as to be the most striking objects in the field. If no cell-form predominates, the growth is called **mixed-celled.**

Next, the *stroma* may present much variety, being mucous, fibrous, cartilaginous, or bony—the mixed forms, **fibro-sarcoma, myxo-sarcoma, chondro-sarcoma,** and **osteo-sarcoma,** resulting.

Lastly, sarcomata may undergo *secondary changes*, which are justifiably described as distinct varieties, inasmuch as the peculiarities are reproduced in the secondary growths. The chief of these are—**melano-sarcoma,** characterized by the development of black pigment, and the very rare form **chloroma,** with green pigment; **lipo-sarcoma,** in which the cells undergo fatty infiltration; **calcifying sarcoma,** in which calcareous infiltration is marked.

PHYSICAL CHARACTERS, ETC.—Portions of sarcomata which have undergone no secondary changes are soft, semi-translucent, grayish, or pinkish gray. These appearances are best seen at the growing edge, which may, however, be very narrow: higher development of the central parts toward one or other form of adult connective tissue may render the recognition of a sarcoma, especially a fibro-sarcoma, difficult—even with the microscope—from the different forms of simple connective-tissue tumors. Degenerative processes, fatty metamorphosis, and especially hemorrhage, may greatly alter the appearances, the latter perhaps converting a solid tumor into a blood-cyst with a scarcely recognizable wall.

As a rule, the growing edge is ill defined, there being no line of demarcation between the tumor and adjacent parts; but sometimes a slowly-growing tumor may acquire a capsule by stretching around itself the connective tissue of the organ in which it originates.

MODE OF GROWTH AND SEATS.—The sarcomata always spring from connective tissue, and may occur wherever connective tissue is present. It is doubtful whether they start from adult tissue

or from some embryonic remnant. Congenital warts and pigment-spots often serve in later life as their starting-points (p. 133). The skin and subcutaneous tissue, fascia, periosteum, medulla, and lymphatic glands are the commonest seats of sarcomata.

CLINICAL CHARACTERS.—The sarcomata occur most frequently in early and middle life, and are among the most malignant of new formations. They are especially characterized by their great tendency to extend locally and to infiltrate the surrounding structures, so that they are exceedingly prone to recur *in loco* after removal. Butlin has shown that sarcomata of certain parts almost always affect lymphatic glands, and early—namely, those of the testis, tonsil, lymphatic glands, and some fasciæ. Those of certain other parts never do, so that, on the whole, sarcomata present a contrast to cancers in this respect. Like cancers they are very liable to become generally disseminated. The secondary growths occur most frequently in the lungs. The dissemination is effected by means of the blood, and is owing to the thinness of the walls of their blood-vessels and to the immediate contact of these with the cells of the growth—conditions most favorable to the entrance of the cellular elements into the circulation. The dissemination of the sarcomata is on this account sometimes more rapid than that of the carcinomata. In the latter extension in the early stage takes place principally by the lymphatics, and dissemination by the blood occurs only later in the disease. The secondary sarcomata usually resemble the primary one, but in exceptional cases the several varieties may replace one another.

These malignant properties, as has been seen, are possessed by the different varieties of sarcoma in very different degrees. As a rule, the softer and more vascular the tumor, and the less its tendency to form a fully-developed tissue, the greater is its malignancy. The soft, round-celled, and large spindle-celled varieties are thus usually much more malignant than the firmer, small spindle-celled growths. Many small spindle-celled tumors after removal never recur, whilst others recur locally several times, and ultimately reproduce themselves in distant parts. As a rule, largeness of the spindle elements and the existence in many of them of more than one nucleus are evidences of special malignancy. Central sarcomata of bone are much less malignant than subperiosteal; the latter, with sarcomata of the tonsil and testis and melanotic sarcoma of skin, being among the most malignant of tumors. The presence of a capsule limiting

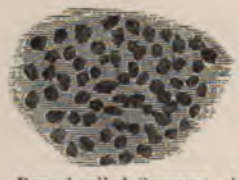
the growth must also be taken into account in judging of the degree of its malignancy. It must, however, be borne in mind that even in a growth distinctly capsuled the sarcomatous elements may invade the adjacent structures. The myeloid growths are the least malignant; they may in exceptional cases give rise to secondary growths in internal organs, but "complete" removal gives a very good chance of non-recurrence. This sometimes occurs with growths having every appearance of malignancy.

The very varying malignancy of tumors having the structure of sarcomata was a main point with Cohnheim in establishing the necessity for diminished physiological resistance before "malignancy" can be manifested.

Round-Celled Sarcoma.

This is of softer consistence than the spindle-celled growths, and from its frequent resemblance in physical characters to encephaloid, it is sometimes known as "medullary," "encephaloid," or "soft" sarcoma. Histologically, it is elementary embryonic tissue, consisting mainly of the round cells already described imbedded in a scanty and usually soft, homogeneous, or finely granular intercellular substance (Fig. 40). The cells usually resemble those met with in the most elementary embryonic tissue; less frequently they are larger, and contain large round or oval nuclei with bright nucleoli. There is an almost complete absence of fusiform cells and of the partial fibrillation which is so frequent in the more highly developed spindle-celled variety.

Fig. 40.



Round-celled Sarcoma: A thin section of a small round-celled sarcoma of the liver. × 200.

The round-celled sarcomata are of a uniform soft, brain-like consistence, somewhat translucent or opaque, and of a grayish or reddish-white color. On scraping the cut surface they yield a juice which is rich in cells. They are exceedingly vascular, the vessels often being dilated and varicose, and from their liability to rupture they frequently give rise to ecchymoses and to the formation of sanguineous cysts. (See "Blood-Cysts.") They grow from the cutis, the subcutaneous cellular tissue, the periosteum, the fasciæ, and the connective tissue of organs. They extend rapidly by peripheral growth, infiltrate the surrounding structures, reproduce themselves in internal organs,

and often involve the lymphatic glands. From their clinical and physical characters these tumors are very liable to be confounded with encephaloid cancer: they are distinguished by the absence of an alveolar stroma and by the penetration of the intercellular substance between the individual cells.

GLIOMA.—This is a variety of round-celled sarcoma growing from the neuroglia or connective tissue of nerve. It consists of very small round cells imbedded in an exceedingly scanty, homogeneous, granular, or slightly fibrillated intercellular substance (Fig. 41).

FIG. 41.

Sarcomatous Tumors from the Brain: *a*. A glioma of cerebellum. This represents the appearance ordinarily presented by these growths. *b*. A comparatively rare form of sarcoma, which consists of large nucleated cells enclosed within the meshes of a vascular network. The development of this tumor took place in the brain subsequently to that of spindle-celled growths—primarily in the thigh, and secondarily in the lung. × 200.

Some of the cells may possess fine prolongations which, by communicating with one another, form a somewhat reticulated structure. These tumors occur in the gray and white substance of the brain, in the cranial nerves, and in the retina. In the retina they usually commence as a minute nodule, which may gradually increase until it projects as a large fungating tumor from the orbit. They are not encapsuled, and although they may occasionally infiltrate the tissues in which they lie and cause secondary growths in their immediate vicinity, they very rarely reproduce themselves in the lymphatic glands or in internal organs. They are liable to small hemorrhages into their structure, and sometimes become more or less caseous.

LYMPHO-SARCOMA.—This is a round-celled sarcoma in which the matrix has developed into a more or less perfect reticulum, like that of lymphoid tissue. It may begin in lymphatic glands or in connective tissue elsewhere. It is distinguished from lymphoma by its more rapid course and by the formation of secondary growths by embolism.

ALVEOLAR SARCOMA.—This is a rare form of round-celled sarcoma which was first described by Billroth. The cells, which are large, sharply defined, round or oval in shape, and enclose prominent round nuclei, are separated from each other by a more or less marked fibrous stroma. In some parts this stroma forms small alveoli within which the cells are grouped; but careful examination will always show that in most parts of the section the stroma really penetrates between the individual cells. It is the last-named character which serves to distinguish these tumors from the cancers, with which in many cases they may easily be confounded. The accompanying drawing, made from a preparation kindly lent to me by Mr. R. J. Godlee, shows well their microscopical characters (Fig. 42). The stroma is often much more delicate, and the cell-masses are more rarely much larger than in the drawing. The cells are in close connection with the stroma. Vessels never pass in among them. Ziegler says the alveolar structure is due to transformation of intervascular tissue into cells whilst the vessels with some connective tissue remain as septa.

FIG. 42.

Alveolar sarcoma: From a tumor of the skin. × 200.

Alveolar sarcomata are met with principally in the skin, bones, and muscles. In the skin, where they are often multiple, they lead to ulceration. They tend to recur locally, and also to reproduce themselves in internal organs.

SPINDLE-CELLED SARCOMA.

These tumors, which include the growths described by Paget in this country as "fibro-plastic" and "recurrent fibroid," are the most common of all the sarcomata. They consist of cells, mainly spindle-shaped and fusiform, separated by only a little homogeneous or slightly fibrillated intercellular substance. These often form whorls round the vessels. The cells, which contain well-marked oval nuclei with one or more nucleoli, are arranged in bundles which pass in all directions through the growth, often giving to it a somewhat fibrous appearance. In those portions of the section in which the bundles of spindle elements have been cut transversely, they present the appearance of round cells. The cells vary considerably in size in different tumors, hence the division into **small** and **large** spindle-celled growths.

SMALL SPINDLE-CELLED SARCOMA.—In these the cells are small, often not more than $\frac{1}{1500}$ inch in length, and the intercellular substance is occasionally imperfectly fibrillated (Fig. 43). These growths approach, therefore, the confines of the fibromata, and histologically they must be regarded as occupying an intermediate place between embryonic and fully-developed connective tissue. They grow from the periosteum, the fasciæ, and from connective tissue in other parts. They are usually tolerably firm in consistence, of a whitish or pinkish-white color, and for the most part present, on section, a translucent somewhat fibrillated appearance. They are often encapsuled, much more frequently so than other varieties of sarcoma, but they are also very liable to infiltrate the surrounding structures and to recur locally after removal.

FIG. 43.

Small Spindle-Celled Sarcoma: From a tumor of the leg. × 200.

LARGE SPINDLE-CELLED SARCOMA.—The cellular elements in these tumors are much larger than in the preceding. The cells are plumper, and the nuclei and nucleoli are especially promi-

FIG. 44.

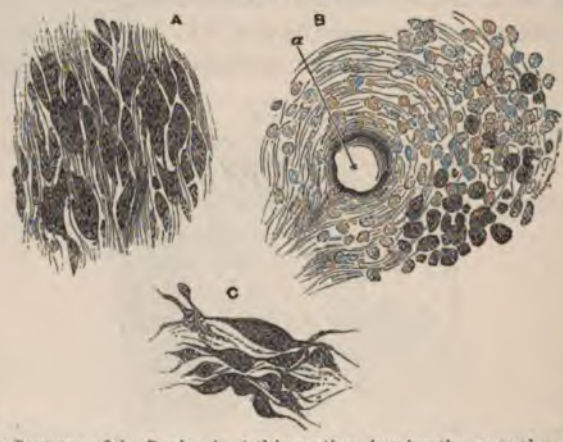
Large Spindle-Celled Sarcoma: To the left, the cells have been separated by teasing, so that their individual forms are apparent; to the right, they are in their natural state of apposition, such as would be seen in a thin section of the tumor. (Virchow.)

nent, and frequently multiple (Fig. 44). The intercellular substance is more scanty, and there is a complete absence of any fibrillation. These growths are much softer in consistence than the small-celled variety. They are of a pinkish-white color, and are often stained by extravasations of blood, and sometimes in parts are almost diffluent from extensive fatty degeneration. They grow rapidly and are usually exceedingly malignant.

MELANOTIC SARCOMA.—This is a variety of sarcoma in which many of the cells contain granules of dark-colored pigment quite distinct from the pigment of extravasated blood. By far the greater number of melanotic tumors are sarcomata, and most of the growths which were formerly described as "melanotic cancers" belong in reality to this class of new formations.

The melanotic sarcomata originate principally in two situations—in the choroid coat of the eye and in the superficial integuments. In both of these situations pigment is a normal constituent of the tissues, and this tendency of structures normally containing pigment to originate melanotic growths is exceedingly characteristic. (See "Pigmentary Degeneration.") These tumors usually consist of spindle-shaped cells (Fig. 45), and hence they are described in the present section; but in some cases the prevailing type of cell is round or oval. The pigment which gives to them their distinctive characters consists of granules of a brownish or dark sepia color, which are distributed

FIG. 45.



A Melanotic Sarcoma of the Penis: A. A thin section showing the general arrangement of the elements. × 200. B. A section from the peripheral part of the growth, showing the "indifferent cells," amongst which are small isolated pigmented elements. At *a* a blood-vessel is seen. × 200. C. Some of the elements separated by teasing. In these the pigment-granules are well seen. × 400.

within the cells (Fig. 45, c), but also in the intercellular substance. Frequently only a very small proportion of the cells are pigmented, whilst in other tumors the pigmentation is much more universal. In all cases, however, a large number of the elements will be found to be quite free from pigment.

These melanotic tumors are amongst the most malignant of the sar-

comatous growths. Although they have comparatively but little tendency to extend locally, they are disseminated by means of the blood-vessels, and occasionally also by the lymphatics, and thus reproduce themselves, often very rapidly, in distant tissues. In doing so, although they almost invariably maintain their melanotic character, the degree of pigmentation of the secondary tumors varies considerably. Whilst many of them may be perfectly black in color, others may be much paler—perhaps only streaked with pigment. The secondary growths are soft, usually distinctly circumscribed, and often encapsuled. They may occur in almost every organ of the body: the liver, the spleen, the kidneys, the lungs, the heart, the brain, and spinal cord, and also the lymphatic glands and subcutaneous tissue, may all be simultaneously involved. I have observed that when occurring in internal organs the pigmentation is not always limited to the secondary nodules, but that many of the cells proper to the organ itself are filled with granules of similar pigment, which is most abundant in the cells immediately adjacent to the new growth. This pigmentation of the cells of the organ often extends for some distance beyond the confines of the tumor.

OSTEOID SARCOMA.—This, which was often called "osteoid cancer," is a variety of sarcoma (usually spindle-celled) in which the growth is either more or less calcified or has partially become converted into true bone. As a primary growth it is met with almost exclusively in connection with bone, growing either from the perios-

FIG. 46.

Calcifying Sarcoma: From a secondary tumor of the lung, showing the calcification of a spindle-celled growth, and the formation of broad bands of calcified intercellular material enclosing spaces which contain round and oval cells. × 200.

teum or the medulla; but the osteoid characters are usually reproduced in secondary tumors occurring in the lungs and other parts.

Calcification is much more common than true ossification; they may occur separately, but are often combined. Bands and patches

of granular appearance, in which the outlines of cells may still be visible or in which all structure has disappeared, and which stain but slightly, show where calcification has occurred (Fig. 46). In other parts, especially near the bone, spicules having the structure of more or less perfect bone—Haversian canals, lacunæ, and imperfect

FIG. 47.

Ossifying Sarcoma of Lower Jaw: *s*. Sarcoma tissue; *b*. new bone, growing from jaw, of which the structure is fairly typical; *p*. point of commencing ossification. Only nuclei of cells are indicated; close to the bone the stroma is very fibrous. × 40.

canaliculi—will be seen penetrating the growth (Fig. 47). The spicules are generally vertical to the surface of the bone. In some cases a skeleton of bony spines radiates from the bone through the growth.

Both calcification and ossification may be very complete, only a thin margin of sarcoma-tissue being left unaffected. In the canals and spaces fibres often develop. A simple osteoma would have cartilage or periosteum on its surface, and would be of much slower growth. It is most important to recognize the difference.

MYELOID SARCOMA.

This, which is the well-known "myeloid tumor," is somewhat allied to the spindle-celled growths. It possesses, however, certain histological peculiarities which probably depend upon the characters of the tissue from which it grows. Myeloid tumors nearly always occur in connection with bone, and most frequently originate in the medullary cavity. They contain many of the large, multinucleated cells already

described as "myeloid cells"—which resemble the cells of the medulla in a state of excessive nutritive activity—together with numerous fusiform cells like those met with in the spindle-celled varieties. There are also some smaller round and oval elements. The large myeloid cells which give to these tumors their distinctive characters are usually much more numerous in those growths which originate in the medullary cavity than in those which spring from the periosteum. These various forms of cells are almost in contact, there being very

FIG. 48.

Myeloid Sarcoma. (Virchow.)

little intercellular substance (Fig. 48). The growths are sometimes very vascular, so much so as to give rise to distinct pulsation. They often contain cysts.

Myeloid tumors almost always grow in connection with bone, the ends of the long bones being their favorite seat. They are also frequently met with springing from the periosteum of the upper and lower alveolar processes, where they constitute one form of epulis. When originating within the medullary cavity the compact tissue of the bone becomes "expanded" over them, and they thus often communicate to palpating fingers the peculiar sensation known to sur-

geons as "eggshell crackling." True expansion of bone is of course impossible; really, the old bone is absorbed from within by the tumor, and the periosteum lays down new bone on the surface; absorption is more rapid than the new formation; the surface layer of bone thins, yields, and crackles under pressure, or is actually wanting at spots where pulsation is marked.

These tumors are for the most part of firmer consistence than the other varieties of sarcoma; many of them are firm and fleshy, although others are softer, more resembling size-gelatin. They are not pulpy and grumous like the soft sarcomata, neither do they present the fasciculated appearance of the spindle-celled varieties. Their cut surface has a uniform succulent appearance, often mottled with patches of red. This red-brown or maroon color (Paget) varies with the number of giant-cells present, and is very characteristic. They are often encapsuled by the periosteal covering of the bone from which they grow. They are rare after middle life, and are the least malignant of all the sarcomata.

Blood-Cysts.

Tumors are occasionally met with into which so much hemorrhage has taken place as to mask their real nature and to give to them the appearance of blood-cysts. The nature of these blood-cysts has only recently been understood. They are now known to be in the majority of cases soft, round, or spindle-celled sarcomata. They consist of broken-down blood-coagula surrounded by an ill-defined layer of soft sarcoma tissue, which is, as a rule, clearly revealed by the microscope. These groups are exceedingly malignant, and hence the recognition of their sarcomatous origin is all important.

CHAPTER XX.

THE MYOMATA, NEUROMATA, AND ANGIOMATA.

The Myomata.

DEFINITION.—The myomata are tumors consisting of muscular tissue.

VARIETIES.—There are two—the striated and non-striated.

1. The **striated myomata** consist of striated muscle. They are exceedingly rare, only two or three examples having been recorded, and these were congenital. Striated cells, generally with non-striated, occur in sarcomata of the kidney and testis found in young children. Striated muscle-cells in congenital growths of organs developed from the Wolffian body are probably due to inclusion in this body of cells from the adjacent muscle-plates.

2. The **non-striated myomata** are most frequent in the uterus; they occur also in the prostate, the œsophagus, and the stomach and intestines. They frequently become pedunculated and form polypi. They are much more common than the striated growths, and probably always originate from muscle. These may form distinctly circumscribed tumors surrounded by a fibrous capsule, or ill-defined irregular masses in the midst of the muscular tissue in which they grow.

They consist, like the physiological tissue, of elongated spindle-cells with rod-shaped nuclei, more or less isolated or grouped into fasciculi of various sizes, with a varying quantity of connective tissue. The muscular elements either present a more or less regular arrangement or pass in all directions through the tumor. The blood-vessels, which are usually not numerous, are distributed in the connective tissue.

SECONDARY CHANGES.—Of these the most frequent is **calcification**. **Hemorrhage, mucoid softening**, and the formation of cysts are occasionally met with; also **inflammation**, ulceration, and necrosis.

CLINICAL CHARACTERS.—Clinically, the myomata are perfectly innocent.

Myoma of Uterus.—The uterus is by far the most frequent seat of myomata, and here they constitute the so-called "uterine fibroid." In most of these muscular tumors of the uterus there is a large proportion of connective tissue; hence the terms "fibroid" and "fibromyoma." This is the case especially in older growths. Those newly developed, however, consist almost entirely of true muscular tissue. They either form firm hard masses imbedded in the uterine walls, or project into the uterine or abdominal cavities. When projecting into the uterus they constitute a common form of uterine polypus. They do not form till after puberty, and are commonest in elderly sterile females. Their growth is usually slow. Pregnancy causes them to enlarge rapidly, and they undergo some involution after delivery.

They generally atrophy at the menopause. These tumors are often multiple. The older ones are liable to become calcified. They also sometimes undergo mucoid softening, which gives rise to the formation of cysts in the tumor.

The Neuromata.*

DEFINITION.—The **neuromata** are tumors consisting almost entirely of nerve-tissue, and are among the rarest of new growths.

The term "**false neuroma**" has been applied to many growths found in connection with nerves—fibrous, myxomatous, and gummy tumors growing within the nerve-sheath having been included under this head. Small multiple fibromata of superficial nerves are sometimes hereditary. The bulbous ends of nerves in stumps are by some called **amputation neuromata.** They often consist only of fibrous tissue, but may contain rolled-up nerve-fibres—attempts at regeneration rather than a tumor. They are usually intimately connected with the cicatricial tissue of the stump.

HISTOLOGY.—The neuromata most commonly consist of ordinary medullated nerve-fibres; they therefore resemble in structure the cerebro-spinal nerves, from which they most frequently grow. The nerve-fibres are associated with more or less connective tissue. Virchow has described, as exceedingly rare formations, also tumors composed of non-medullated fibres and of ganglionic nerve-tissue.

SEATS.—The **true neuromata** always originate from pre-existing nerve-tissue, either from the cranial or from the spinal nerves.

PHYSICAL CHARACTERS.—Neuromata rarely attain a large size, but usually exist as small, hard, single nodules.

CLINICAL CHARACTERS.—Clinically, the neuromata are perfectly innocent tumors. They often cause considerable pain. Their growth is slow.

The Angiomata.

DEFINITION.—The angiomata, or vascular tumors, consist of blood-vessels held together by a small amount of connective tissue.

* If, as seems probable, nerves are outgrowths from the cerebro-spinal centre, the neuromata should be classed as epiblastic growths.

VARIETIES.—They include the various forms of nævi and aneurism by anastomosis. They may be divided into two classes—the **simple** or **capillary** angiomata, in which the new vessels resemble chiefly normal capillaries; and the **cavernous** or **venous** angiomata, in which the blood circulates in a cavernous structure similar to that of the corpus cavernosum penis. The characters of both are well shown in the accompanying drawings, made from specimens kindly lent by Mr. Boyd.

1. **Simple Angiomata.**—These consist of tortuous and dilated capillary vessels, held together by a small quantity of connective and adipose tissue (Fig. 49). It is doubtful what proportion of the ves-

FIG. 49.

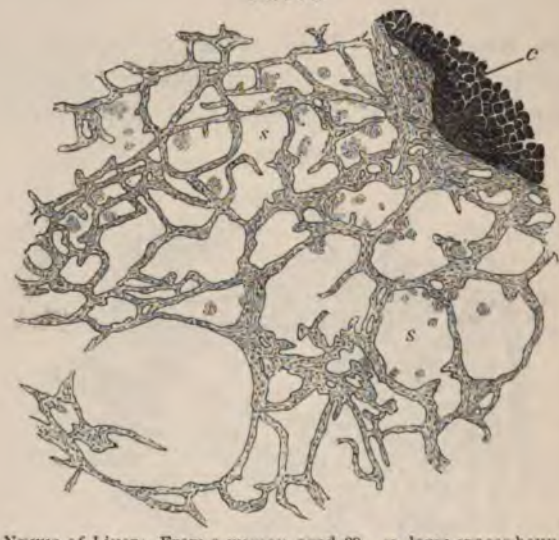
Capillary Nævus from Subcutaneous Tissue of a Child: *cap.*, vessels of new growth: *a.* normal artery; *f.* fat-cells; *c.* capsule. × 200, reduced ½.

sels is due to dilatation of the original capillaries, but Ziegler thinks that many are formed this way. Some are of new formation. Very irregular dilatations are common. The capillary walls may be thin or thick, consisting of a double tier of cells. One or two supplying arteries can be seen in most sections. These growths generally occupy the superficial layers of the cutis, and form the port-wine stains and mother's marks; they are slightly or not at all elevated. Others lie in the subcutaneous or submucous tissue, and may form large tumors. Their color is red, violet, or purple, according to the depth of the vessels and the rate of flow through them; the most frequent color is red when superficial, bluish when subcutaneous. They are probably always congenital, though they may not be noticed for a few minutes after birth.

Simple angioma is often combined with lipoma, glioma, sarcoma. Sometimes cysts containing dark fluid form.

2. **Cavernous Angiomata.** — These are the venous vascular tumors. The growth is made up of irregular fibrous alveoli, which communicate freely with one another, and are lined with an endothelium similar to that of the veins (Fig. 50). These spaces are dis-

FIG. 50.



Cavernous Nævus of Liver: From a woman aged 39. *ss.* large spaces bounded by fibrous walls, some containing blood-débris; *c.* liver-cells (too large) toward which the growth is bounded by thick fibrous walls. × 40, reduced ⅓.

tended with blood, which is supplied to them by numerous vessels and circulates with varying degrees of rapidity. The arteries open directly into the spaces. These growths are commonly of bluish color. They may be diffuse or form distinctly circumscribed tumors. They sometimes exhibit distinct pulsation. Their favorite seat is the skin and subcutaneous tissue. They may occur also in the orbit, muscle, liver, spleen, and kidneys. They may develop by dilatation of the vessels of a simple angioma. They may be congenital, but in the liver Ziegler thinks they develop after middle age, when the cells begin to atrophy.

ANEURISM BY ANASTOMOSIS.—The arteries of an area, especially on the head, become dilated, greatly elongated, and tortuous; perhaps new vessels form. Some are congenital, others follow injuries.

CHAPTER XXI.

THE PAPILLOMATA.

DEFINITION.—The papillomata are new formations resembling in structure ordinary papillæ.

HISTOLOGY.—They consist of a basis of often richly cellular connective tissue, which sends toward the surface numerous papillary processes, each supporting blood-vessels which end in a capillary network or single loop, the whole being enveloped in a covering of epithelium. The papillæ may be short and simple as in an ordinary wart, or they may be long, delicate, branching, giving off secondary and tertiary offsets, and very numerous, as in villous tumor. The covering epithelium in skin-growths is thick, hard, and stratified, and may actually bind the papillæ into a solid mass; but on mucous membranes the slender vascular processes are covered by delicate epithelium, and they are consequently easily lacerable. Warts on serous membranes have often for covering only a single layer of endothelial cells.

SECONDARY CHANGES.—Hemorrhage and ulceration resulting from injury can hardly be classed under this head; so the only important change is that to epithelioma. In a wart all the epithelium is on the surface—no matter how irregular that surface may be—of the cutis: once the epithelium begins to invade the latter, the wart has become a cancer. Pigmented warts not uncommonly form on the face in old age, and it is as well to watch, but *not* to irritate, them.

VARIETIES.—1. The ordinary skin-wart with its covering of hard squamous epidermis. Condylomata and venereal warts, from the irritation of the secretions of soft sores or gonorrhœa, deserve special mention. These, though covered by squamous epithelium, are much softer, more vascular, and more luxuriant in growth than the ordinary skin-wart. They affect warm, moist parts. 2. The soft

warts and villous tumors of all mucous surfaces, characterized usually by long, delicate compound papillæ, the tongue and cheek, the larynx and the bladder, being most often affected. 3. **Corns** commence as papillomata, but as the epidermis thickens and is pressed into the soft parts by the boot the papillæ ultimately atrophy. 4. **Horns** some

FIG. 51.

Section of Wart on Skin of Abdomen: *e.* epithelium; *c.t.* connective tissue continuous with epidermis and cutis; *s.* accumulations of horny epidermis deep down between the papillæ, looking in section like large nests. × 10.

inches long occasionally spring from parts of the skin: they consist of epithelium and sebaceous secretion, and originate from sebaceous follicles or from a sebaceous cyst. It is said that long papillæ project into their bases, so they seem to be allied to warts. The base must be removed with the horn or it will recur.

PHYSICAL CHARACTERS.—The ordinary wart is a hard, abruptly elevated little mass, apparently of epithelium, presenting an irregular ("warty") surface often divided by deep fissures. If the investing epithelium be abundant or the papillæ be very short, a rounded mass having a merely furrowed surface results; but as the papillæ lengthen and the epithelium thins, the growth presents first a cauliflower, then a branched, and finally a villous, appearance. The latter appearance is best seen on placing a "villous tumor" of the bladder in water, when the delicate long papillæ float up. They are exceedingly vascular. Papillomata of serous membranes occur usually as small outgrowths from synovial membranes in chronic joint diseases. On section of a papilloma the relation above described between stroma and epithelium is seen, even with the naked eye.

SEATS.—Papillomata always originate from skin, from mucous or serous membranes. They most frequently grow from pre-existing papillæ; sometimes, however, they occur where no papillæ exist, springing directly from the subepithelial connective tissue: this is the case in the stomach and larynx. As all new growths on free surfaces tend to become "papillary," it is probably the result of physical conditions. A wart would thus be a fibroma become papillary by an accident of position, and papillomata as a class would disappear.

CLINICAL CHARACTERS.—Warts, pathologically speaking, are quite innocent. They occur in childhood and early adult age chiefly, especially upon the hands and face. They may be single, but upon the hands are commonly multiple; they generally disappear after a time, often years. Warts on mucous surfaces give trouble, and may cause death by bleeding: in the bladder difficulty may arise from obstruction to the inflow or outflow of urine, the urethral orifice being a favorite seat. Lastly, the tendency of warts and warty surfaces (ichthyosis linguæ) to become epitheliomatous in advanced life must be remembered.

CHAPTER XXII.

THE ADENOMATA.

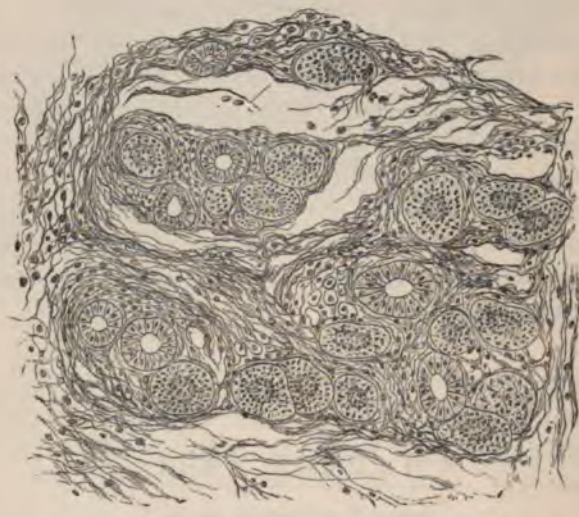
DEFINITION.—The adenomata—or, as they are more commonly called, **glandular tumors**—are new formations of gland-tissue more or less atypical in structure, having an abnormal relation to the tissue around it, and incapable of performing the function of the gland they imitate. Their ducts do not enter those of the gland whence they spring.

HISTOLOGY AND VARIETIES.—In structure the adenomata resemble the racemose or tubular glands.

1. The **racemose adenomata** consist of numerous saccules or acini lined with small epithelial cells, which are often two or three layers deep. The acini communicate with each other and are grouped together, being separated merely by connective tissue, in which are

contained the blood-vessels. The connective tissue varies in amount; when much in excess of the normal the growth is called an **adeno-fibroma.** It may resemble the normal tissue, or, if growing rapidly, it will be much more richly cellular, containing round and spindle elements: absolute anatomical distinction between such growths and sarcomata is impossible. The structure of these tumors is well shown in the accompanying drawing from a specimen kindly lent by Mr. Cantlie (Fig. 52).

FIG. 52.



Adenoma of Mamma. × 200, reduced ½.

All growths originating in glandular organs may be associated with more or less glandular structure. In the mamma, for example, sarcoma, myxoma, and other forms of tumor are often so intermingled with the gland-tissue of the organ that it becomes difficult to say which is the predominant structure. In many cases it is evident that the development of such tumors is accompanied by an increase of the gland-tissue amongst which they grow. Thus are produced mixed forms—**adeno-sarcoma, adeno-myxoma, etc.** These are not adenomata, because the stroma is not that of normal gland.

1. The **tubular adenomata** grow from mucous membranes, and consist of groups of tubules lined with epithelium. They will be again alluded to hereafter.

DEVELOPMENT.—The adenomata almost always orignate from pre-existing gland structures. They generally grow slowly, and probably from some hitherto quiescent congenitally misplaced rudiment; otherwise it is difficult to explain the complete encapsulation and separation from the normal gland which distinguish adenoma from localized hypertrophy. The latter swelling remains in intimate relation with the gland, and is probably often of inflammatory origin.

SECONDARY CHANGES.—The most frequent of these is **fatty degeneration** of the epithelium, which may give rise to the formation of small caseous masses in the growth. Dilatation of the saccules and tubules into **cysts** and **mucoid softening** are also common. The origin of cancer has several times been traced to an adenoma.

SEATS.—The word "adenoma" has been loosely used, as above pointed out, so as to include all new formations of gland-tissue. It is described as occurring in the following organs:

Mamma.—This is much the most common seat of adenoma, or

FIG. 53.

Adeno-fibroma of Mamma: Showing new growth of gland-structure and of connective tissue. × 100, reduced ⅓.

rather of adeno-fibroma; for a glandular tumor which is structurally indistinguishable from normal breast is very rare (Fig. 52). The

arrangement of the epithelium, the number and size of the spaces, the proportion of stroma, and the number of cells it contains, is more or less abnormal (Fig. 53); hence the second name is generally most applicable. These tumors are called also "chronic mammary" and "adenoid." They are encapsuled; round, oval, or lobulated; lying in or on the breast. They are of hard, elastic consistence; their section is convex rather than cupped, of fibrous appearance, often lobulated, or showing distinct slits and a racemose structure even to the naked eye. These tumors are most common in early life. They may be multiple. Many adeno-fibromata contain cysts, which may be very numerous and vary in size from slight dilatations of ducts and acini up to cavities holding some ounces. They contain yellow mucoid fluid, which may be reddish or brown from extravasated blood. Many are lined with cylindrical epithelium like that of the gland-spaces, but others appear to be formed by localized softenings of the stroma. At first they appear on section like irregular and branched fissures, then like spaces full of fluid; but in other cases these are almost completely filled by papillary fibrous growths covered by cubical epithelium which grow in from their wall. These cystic growths are called **cystic adenoma,** or, if the stroma is richly cellular, **cystic adeno-sarcoma.**

The non-cystic growths must be distinguished from local and general hypertrophies of the gland.

Ovary.—Many compound ovarian cysts are really cystic tubular adenomata, and often contain papillary growths (Fig. 54).

Testis.—No pure adenomata, but mixed tumors, like those in the parotid, occur.

Prostate.—Some of the tumors which form in this body in advanced age contain glands as well as muscle and connective tissue (adeno-myoma).

Thyroid.—Apart from the hypertrophy of endemic goitre and Graves' disease, distinct encapsuled tumors having the structure of the thyroid occur in its substance.

Parotid.—Pure glandular tumors are infrequent, and the gland-epithelium is generally very atypical. Fibro-adenomata are commoner; but the ordinary "parotid tumor" is "mixed," containing cartilage, mucous tissue, etc. The other salivary glands are much more rarely affected.

Liver.—Small encapsuled tumors having the structure of the liver are rarely found.

Glands of Mucous Membranes.—Racemose glands—mucous, Brunner's—may hypertrophy like the above. Gland-tissue enters largely into the structure of some of the "mucous" polypi which spring from every mucous membrane, especially in catarrhal states. In some cases the glands probably enlarge primarily, project, and become polypoid. In other cases it is thought that localized increase of connective tissue from inflammation may necessitate increase of the epithelial structures in relation with it. Polypi of the nose, stomach, intestines, rectum, and uterus are examples. The connective tissue is

FIG. 54.

Papillary Growth inside an Ovarian Cyst, projecting from its wall (*w*): They consist of loose connective tissue (*c*), containing many branched cells, covered by a layer of columnar cells (*e*). Secondary processes are numerous (*p*). × 40, reduced ⅔.

soft and œdematous; the surface is covered by the epithelium of the part.

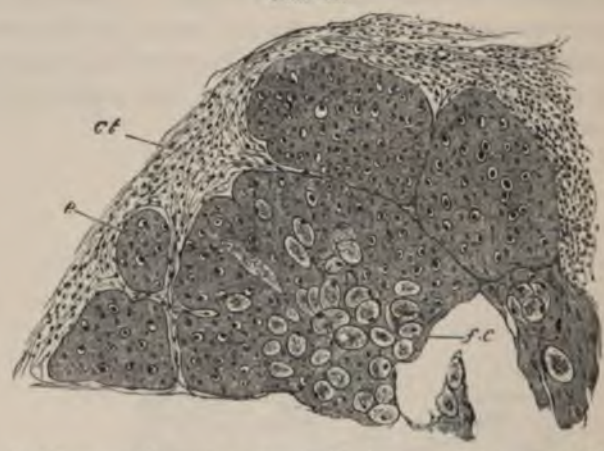
Sebaceous and Sweat-Glands.—"Adenomata" of these are hypertrophies rather than tumors, being uniform enlargements of the glands. Fig. 55, from a specimen of Mr. Boyd's, shows a small portion of a sebaceous "adenoma" from the chin of a child.

Calcification of the epithelial masses may occur, and Malherbe has shown that ossification of the fibrous stroma may also take place; such tumors are rare, and have been called "osteomata" of the skin.

Adenomata afford further support to Cohnheim's view concerning

the nature of malignancy (p. 131). Almost invariably an adenoma or adeno-fibroma proves perfectly innocent. But now and again cases occur which appear clinically and microscopically to be ordinary adenomata, but which recur locally after removal. It is no explana-

FIG. 55.



Lobule of a Sebaceous Adenoma: *c.t.* Connective tissue containing many cells, and forming capsule and septa. *e.* Saccule full of epithelial cells, few of which show signs of fatty degeneration—a clear space, pushing nucleus aside. In larger saccules degeneration is more general and extreme (*f.c.*). × 200.

tion to call these sarcomata. Again, there are several cases on record of generalization of tumors having the structure of normal thyroid; also some of ovarian adenoma.

The lumina of racemose adenomata are sometimes filled up with epithelial cells; it is then impossible to distinguish them microscopically from scirrhus in its earliest stage—that of multiplication of epithelium. Indeed, the origin of cancer from adenomata has several times been proved microscopically and clinically.

As sarcoma-tissue passes insensibly into fibrous, it is often impossible to say with certainty which name—adeno-fibroma or adeno-sarcoma—should be applied to the stroma of a tumor containing gland-tissue.

CHAPTER XXIII.

THE CARCINOMATA.

DEFINITION.—The carcinomata or cancers are most atypical new formations of cells of the epithelial type, grouped irregularly in the alveoli of a more or less dense fibroid stroma. The "epithelial type" implies origin from epi- or hypoblast, and the absence of intercellular substance; it does not imply any specific form of cell.

The alveolar structure, seen on section, has caused it to be said that cancer is an atypical gland-structure. Every tumor is atypical morphologically and physiologically; almost all are so structurally. In cancer we have epithelial cells, often of the most abnormal form, filling up the lumina of gland-tubes (if it start from a gland), bursting through their basement or limiting membrane, and ramifying in the spaces of connective tissue. The only type for such a process as this is the development of a gland (like the liver) by growth of solid hypoblastic rods into a mesoblastic stroma.

HISTOLOGY.—The definition shows that we have to describe, first, the epithelial cells; and, secondly, the stroma which forms the spaces in which they lie.

The **cells** are characterized by their large size, by the diversity of their forms, and by the magnitude and prominence of their nuclei and nucleoli (Fig. 56). They are round, oval, fusiform, caudate, polygonal—exhibiting, in short, every diversity of outline. These variations in form are principally owing to the mutual pressure to which, in their growth, they are subjected. The nuclei are large and prominent, round or oval in shape, and contain one or more bright nucleoli. The nuclei are perhaps most frequently single, but two are often met with, and in the softer and more rapidly growing cancers there may be more. The cells lie loosely in the alveoli; no stroma passes between them. The cells rapidly undergo retrogressive changes; hence they usually contain

FIG. 56.

Cells from a Scirrhus of the Mamma. × 350.

molecular fat. Sometimes so many have been destroyed that more free nuclei than cells are visible. Cells precisely similar to these are met with in other morbid growths, and also in the normal tissues. There is thus no *specific* "cancer-cell."

The **stroma** varies considerably in amount, being much more abundant in some specimens than in others. It consists of a more or less distinctly fibrillated tissue arranged so as to form alveoli of various forms and sizes, within which the cells are grouped (Figs. 57 and 59). It is not closely connected with the cells, and none penetrates between them. These alveoli communicate with one another, so as to form a continuous cavernous system. The characters of the stroma vary with its rate of growth: if this is rapid, it will contain some round and spindle-shaped cells (see Figs. 61 and 66); if, on the other hand, it is slow or has altogether ceased, the tissue will contain few or no cells, and will be denser and more fibrous in character (Fig. 59). The latter is the condition in which it is most commonly met with.

FIG. 57.

The Alveolar Stroma from a Scirrhus of the Mamma: The cells have been removed by pencilling. × 200.

In the stroma are the **blood-vessels.** These are often very numerous, and form a close network round the alveoli. They are limited to the stroma, and never pass into the epithelial masses. This distribution of the blood-vessels is important, as distinguishing the carcinomata from the sarcomata, excepting some alveolar sarcomata and tumors springing from endothelium.

Lymphatics have been shown by MM. Cornil and Ranvier to communicate freely with the alveoli. This explains the great tendency of cancer to infect the lymphatic glands. In fact, the alveoli may be regarded as dilated lymphatics, for the epithelial columns grow along lymphatic spaces—the lines of least resistance.

DEVELOPMENT.—The question of the genesis of carcinoma involves that of the genesis of epithelium generally. It is maintained by most histologists that epithelium can originate only from epithelium, and that the epiblast and hypoblast are the sources from which all epithelium is subsequently derived. Others state that epithelium may originate also from connective tissue. A like difference of opinion

exists as to the source of the epithelioid cells of cancer. By many—as Waldeyer, Thiersch, and Billroth—they are regarded as originating only from pre-existing epithelium. Others—amongst whom are Virchow, Lücke, Rindfleisch, and Klebs—maintain that they may be derived also from cells belonging to the connective tissue. It is also believed by some—as Köster—that many cancers originate from the endothelium of the lymphatics; *i. e.* specialized connective-tissue corpuscles.

Nearly all modern observations tend to support the epithelial origin. This renders it impossible for true cancer to develop in any mesoblastic structure. Cases have been reported of primary cancer in lymphatic glands, in bone, in the membranes of the brain, etc. Here either some small primary growth which gave rise to no symptoms has been overlooked, or some abnormality has existed, such as a detached piece of mamma lying near the axillary glands or fœtal inclusion of an epithelial rudiment; or the growth was one of those sarcomata which can be distinguished from true cancer only by the closest examination, or even by working out their development (alveolar sarcomata, cylindromata).

Epithelial cells are said to occur round a cancer, but quite isolated from it, lying in connective-tissue spaces. This isolation is very difficult to prove, and does not necessitate the origin of the cells from connective-tissue elements. For they may have been carried by the lymph-stream, aided by the spontaneous movement noted in cancer-cells by Carmalt. Often delicate chains of cells one to two inches long have been traced between a main growth and an apparently isolated nodule; such a chain might easily be interrupted. With better appliances and more careful work the reported cases of primary mesoblastic cancer are getting fewer and fewer.

It is most probable, therefore, that a cancer originates either in the growth of a resting embryonic epithelial rudiment (Cohnheim) or in the multiplication of some epithelial cells. Other conditions being favorable (see "Malignancy"), the cells burst through any basement membrane, and grow in the connective tissue along lymph-spaces and channels. We then have epithelial cells lying actually in the lymph-current, where they would naturally multiply very rapidly, being bathed in nutrient fluid; so glandular infection is easy to explain. Where resistance is great, the growing cell-columns are narrow; where it is slight, they widen out.

The connective-tissue bundles of the part at first alone form the

stroma, but round-celled infiltration, probably the result of more or less intense inflammation excited by the epithelial invasion, soon appears. The round cells probably form fibroid tissue which contracts. At first other elements of the part may persist in the stroma—*e. g.* fat-cells in the breast, plain muscle-fibre in the prostate.

With this mode of growth the carcinomata never become encapsuled, but gradually infiltrate surrounding structures. This process of infiltration is very characteristic, and is more marked in cancer than in any of the malignant growths. A zone of small-celled infiltration is seen for some distance around the confines of the tumor, so that there is no line of demarcation between it and the normal structures. (See Fig. 58.)

SECONDARY CHANGES.—The most important of these is **fatty degeneration.** This always occurs to a greater or less extent in all the varieties of carcinoma. The more rapid the growth, the earlier does this retrogressive change take place and the greater is its extent; hence it is usually most marked in encephaloid. It produces softening of the growth, which is often reduced to a pulpy, cream-like consistence. **Hemorrhage, pigmentation, mucoid** and **colloid degeneration,** may also occur, with cyst-formation. Cysts may be due also to blocking of ducts—*e. g.* in the mammæ. **Calcification** and true **ossification** are very rarely met with. Formation of an **abscess** is rare, but important.

VARIETIES.—The cells vary markedly in character according as they spring from stratified epithelium, columnar epithelium, or the epithelium of acinous glands. They inherit to a greater or less extent the form and tendencies of the variety of epithelium from which they originate. Thus, cells of cancers springing from stratified epithelium tend also to undergo the ordinary epithelial evolution, ending in cornification; and in many cases they show prickle-cells. Columnar epithelium often retains its typical form, and continues to surround open spaces; but in other cases the cells multiply so as to fill the spaces, the outermost cells generally retaining a cylindrical shape. Cells of acinous glands undergo no evolution; by multiplication they produce cells of their own kind, which may be much altered in shape by mutual pressure. Upon the retention by the cells of ancestral characters the chief varieties of cancer are based—the **squamous** and **columnar-celled epithelioma** and **acinous cancer.** But ancestral

peculiarities are not always retained. Certain cancers springing from stratified epithelium—perhaps from the small glands in relation with it—undergo no evolution, and are indistinguishable from scirrhus; and tumors springing from columnar epithelium are in many parts exactly similar to acinous cancer.

In all varieties of carcinoma the secondary growths tend to repeat the peculiarities of the primary, especially in epithelioma. In scirrhus the secondary growths in internal organs, though sometimes resembling the primary tumor, are often more rapidly developed, are softer and more vascular, and, in accordance with the artificial distinction which has been made between scirrhus and encephaloid, they must be regarded as belonging to the latter variety of cancer.

The name "epithelioma" was given to cancers springing from the epithelia, in opposition, as it was thought, to the cancers of connective-tissue origin. The distinction of the forms is of much less importance now that the epithelial origin of all is coming to be more and more recognized. Still, the histological differences between well-marked cases are sufficient to justify a separate description of the above varieties.

We accordingly divide carcinomata into two chief groups: **acinous cancer**, with *scirrhus* or *chronic cancer* and *encephaloid* or *acute cancer* as subdivisions; and **epithelial cancer**, including *squamous* and *columnar-celled epithelioma*. **Colloid** or **gelatiniform cancer**, due to colloid degeneration of the cancer-cells, was formerly regarded as a subdivision of acinous cancer or even as a separate variety; but all the above varieties occasionally undergo this degeneration.

CLINICAL CHARACTERS.—Cancers occur with increasing frequency after thirty-five; below thirty they are rare tumors. They are almost always primarily single. They are among the most malignant tumors, there being little ground for choice between them and the sarcomata as regards their mortality. As a group the cancers grow rapidly, infiltrate surrounding parts widely, frequently ulcerate and give rise to most offensive sores which bleed readily, infect lymphatic glands early (p. 182), and ultimately become disseminated widely throughout the system. Unless very early and freely excised they recur *in loco*.

It will be remembered that the sarcomata as a group do not infect lymphatic glands (p. 159), but, on the other hand, it is said that sarcomata generalize earlier and more readily—the sarcoma-cells fre-

quently forming the very walls of the vessels, whilst the cells of cancers do not come into contact with their vessels.

Just as the sarcomata vary in malignancy, so also do the carcinomata. On the whole, encephaloid is more speedily fatal than scirrhus, owing to its more rapid growth, greater vascularity, and more active epithelial elements. Colloid degeneration seems to diminish malignancy. Every now and again a tumor is met with, especially in the soft palate, encapsuled and showing no sign of malignancy, yet having the structure of acinous cancer. In the variety known as atrophic scirrhus the duration of the disease is not uncommonly from ten to twenty years, and the extension only local and glandular.

Epithelioma is, pathologically, much the least malignant cancer. It extends locally, ulcerates early, and often infects the neighboring lymphatics, but comparatively rarely reproduces itself in internal organs. This is probably owing to the size and character of its epithelial elements, which render them much less liable to be transmitted by the blood- and lymph-streams than are the cells of the other varieties of cancer. Its malignancy varies curiously with its seat; thus, on the skin of the face epithelioma has generally a very chronic course, and rarely affects even the glands; on the lip, early excision gives a fair chance of cure; on the tongue, its course is often so rapid, affection of the glands so early, and cachexia and death so speedy, that it must be ranked as one of the most malignant tumors.

Acinous Cancer.

1. **SCIRRHUS** or **CHRONIC CANCER** is characterized by the amount and density of its stroma and by the slowness of its growth as compared with that of encephaloid. The latter point probably accounts in great measure for the peculiarities in its structure and physical characters.

The epithelial growth, although at first it may be luxuriant, quickly subsides. The elements soon atrophy and undergo fatty metamorphosis. They are most abundant in the external portions of the tumor, where growth is taking place; in the central portions they may be almost entirely wanting. Figs 58 and 59 show the appearances presented by scirrhus of the mamma in the earlier stages of its development.

The degeneration of the epithelial elements is probably due to obliteration of vessels by scar-like contraction of the stroma, which

quickly becomes hard and indurated: development of the cancer is thus arrested. The whole of the central portions of the growth may

FIG. 58.

Scirrhus of the Mamma: A section through the edge of the tumor, showing the small-celled infiltration of the muscular fibres and adipose tissue in the neighborhood of the gland. × 200.

thus ultimately consist simply of dense fibroid tissue, amongst which are contained atropical epithelial cells and fatty débris (Fig. 60),

FIG. 59.

Scirrhus of the Mamma: A portion of the tumor somewhat internal to that represented in Fig. 58, showing the characteristic alveolar structure of the cancer. × 200.

the periphery being the only part where the epithelial structure is visible. The amount of atrophy and contraction varies considerably in different cases.

FIG. 60.

a *b*

Scirrhus of the Mamma: A section from the more central portions of the tumor, showing the atrophy of the epithelial cells, the diminution in the size of the alveoli, the fibroid tissue, and the fatty debris; *a*. Earlier stage; *b*. More advanced. × 200.

The physical characters of scirrhus are in the same way due to the abundance of its stroma. The growth is firm and hard, and is usually depressed in the centre, owing to the contraction of the fibroid tissue and atrophy of cells. This is very characteristic of scirrhus of the breast, where it causes retraction of the nipple and

puckering of the skin. The growth is very hard, and creaks under the knife. The surface of the section is generally "cupped," and of grayish-white, semi-translucent appearance ("like an unripe pear"), more or less mottled with dots and streaks of opaque yellow, due to fatty epithelium in alveoli or milk-ducts. The latter may be cystic. The central parts are pale and fibroid; the more external are pink, because contraction has not obliterated the vessels, and less firm than the central portions of the growth. They yield, on scraping, a juice which is rich in nucleated cells, free nuclei, and granules.

Scirrhus is by far most commonly met with in the female breast, rarely in the male breast; in the stomach, liver, pancreas, and prostate; in the skin and mucous membranes, starting from racemose mucous glands. The secondary growths to which it gives rise are often encephaloid.

2. **ENCEPHALOID**, or **ACUTE CANCER**, differs from the preceding merely in the greater rapidity of its growth and the consequent small amount of its stroma and the softness of its consistence. Encephaloid and scirrhus cannot be regarded as in any way constituting distinct varieties of carcinoma. There are all intermediate stages between them (scirrho-encephaloid), and their structural and clinical differences are accounted for by differences in rapidity of growth, which probably depends upon the vascularity of the part in which they are situated.

Fig. 61.

Encephaloid Cancer, from a secondary cancer of the liver, showing the large size of the alveoli and the thinness of their walls. In the latter small cells are visible. The large epithelial cells are commencing to undergo fatty metamorphosis. × 200.

The epithelial growth in encephaloid is rapid and abundant; the cells, which may be either larger or smaller than those in scirrhus, quickly undergo fatty degeneration, so that often more free nuclei than cells are visible.

The proportion of stroma is very small, and, owing to the rapidity of its growth, it is much less fibrous than that of scirrhus, and does not undergo a similar cicatricial contraction (Fig. 61). The blood-vessels are often very abundant, and, the tissue supporting them being soft and non-resistant hemorrhage occasionally takes place.

Encephaloid cancer is of a soft, brain-like consistence, the central portions, where fatty degeneration is most advanced, often being completely diffluent. The tumor is sometimes more or less lobulated. On section the undegenerate parts are gray, pinkish, soft, and translucent, whilst the degenerate form a white pulpy mass much resembling brain-substance, which is often irregularly stained with extravasated blood.

Encephaloid is much less common than scirrhus cancer. It is most frequently met with in internal organs as a *secondary* growth. It is sometimes *primary* in the testis and mamma. It may fungate and bleed (fungus hæmatodes). Many growths formerly described as encephaloid cancer are soft sarcomata. (See p. 160.)

Epithelioma.

1. **SQUAMOUS EPITHELIOMA** constitutes a tolerably distinct variety of carcinoma, but transitional forms between it and scirrhus are occasionally met with. It always grows from a surface covered by squamous epithelium, either cutaneous or mucous (the junction of the two being a common seat), and its epithelial elements closely resemble that of squamous epithelium.

The cells (Fig. 62) are often considerably flattened and distorted in shape, owing to the pressure to which, in their growth, they are subjected. The cells grow down from the surface-epithelium into the lymph-spaces of the connective tissue, and, pushing their way along these, are formed into solid cylinders which twist about, branch, and intercommunicate—swell out at some points, become constricted or even interrupted at others. Single epithelial cells may be recognized here and there, evidently swept on by lymph. The rods cut across appear as round or oval masses of cells, of which the outermost are usually large, whilst the central are more or less squamous and form a yellowish onion-like mass. Sometimes the central cells appear large and vesicular, whilst the outermost are scaly and flattened. These concentric masses of cells are called "concentric globes," or "epithelial nests," and, though not distinctive or essential, they are exceedingly characteristic of epithelioma. The cells are

Fig. 62.

Cells from an Epithelium of the lip. × 250.

usually fatty, and may be so closely packed as ultimately to become hard and dry like those of the nails and hair, and the globes are then of a brownish-yellow color and of a firm consistence. The globes are often large enough to be readily visible to the naked eye, and, owing to the onion-like arrangement of the epidermic scales, they usually present a fibrous appearance.

The stroma presents every variation between rapidly-growing embryonic and an incompletely fibrillated tissue. It may be tolerably abundant or almost entirely wanting. It rarely forms such a marked alveolar structure as that which characterizes the other varieties of carcinoma, and consists simply of fibrous tissue of the part more or less infiltrated with small round cells, which may ultimately develop into connective tissue (Fig. 64).

FIG. 63.

Epithelioma of the Lips, showing the concentric globes of epithelial cells. × 100.

The development of epithelioma takes place by down-growth of the surface-epithelium of skin or certain mucous membranes into the connective tissue and deeper parts, just as is described on p. 185 (Fig. 64). The tendency of epithelioma is to ulcerate early: this is due to fatty degeneration of the cells, and not to inflammation.

Epithelioma usually presents itself, in the first place, either as a small hard ulcer, as an indurated fissure, or as a subcutaneous induration or nodule which subsequently ulcerates. The surface of the

ulcer is irregular, and may be sloughy; often it is clean, and covered by large, firm, bluish-red granulations, consisting largely of epithelium; more rarely the surface is markedly warty. The tumor itself is firm in consistence, often more or less friable, and on section presents a grayish-white granular surface, sometimes intersected with

FIG. 64.

Epithelioma of the Tongue: A vertical section, showing excessive epithelial growth upon the surface of the papillæ and extension of the cells into the subjacent connective tissue. The subepithelial tissue is infiltrated with small cells, among which are epithelial cells both single and forming concentric globes. × 100.

lines of fibrous tissue. The cut surface yields on pressure a small quantity of turbid liquid, and in many cases also a peculiar, thick, crumbling, curdy material can be expressed, which often comes out in a worm-like shape, like sebaceous matter from the glands of the skin. This latter is very characteristic. It is composed of fatty epithelial scales, and on being mixed with water it does not diffuse like the juice of other cancers, but separates into minute visible particles. If

it is very abundant, the cancer is soft and friable, and the material can be seen on the cut surface as small scattered opaque dots.

Irritation has more to do with the causation of epitheliomata than of other kinds of cancer. Some, as sweeps' cancer of the scrotum from soot, and epithelioma of the arm of workers with tar or paraffin, appear to be due simply to irritation in people the physiological resistance of whose connective tissue is sufficiently diminished by the irritation or otherwise to permit invasion. Other epitheliomata occur at those spots at which, the process of development being complicated, errors are likely to occur; resulting, as Cohnheim supposes, in the formation of a resting, embryonic rudiment. Such spots are—the lower lip, tongue, ala nasi, eyelid, cervix uteri, gullet where crossed by bronchus, etc. (See p. 134.) Many of these are points exposed to irritation. It usually infects the lymphatic glands, but rarely occurs in internal organs.

Rodent Ulcer.

RODENT ULCER deserves a short notice. It is a form of epithelioma beginning usually as a pimple upon the nose or cheek, and liable to frequent irritation from rubbing, picking, etc. After a time it ulcerates and the ulcer slowly spreads, destroying everything, including bones, that it meets, and producing the most hideous deformity. This may go on for many years, the health remaining good and no gland being affected. It differs from ordinary squamous epithelioma

Fig. 65.

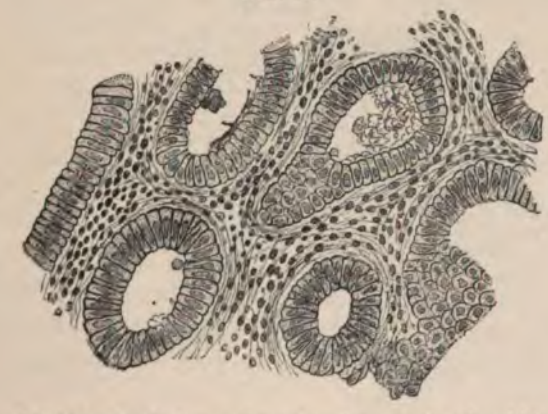
Rodent Ulcer of Nose: The patient had small rodent ulcers of the nose and cheek and an early epithelioma of the lip. × 50.

chiefly in the small size of the cells, the absence of prickle-cells, the slight tendency they show to become scaly, and the consequent infrequency

of nests, and the ease with which the epithelial columns can be traced (Fig. 65). Some believe that rodent ulcer begins from the root-sheaths of the hairs or from some gland-epithelium of the skin. In some cases having the characteristic history of rodent ulcer the structure is that of typical epithelioma.

2. **COLUMNAR-CELLED EPITHELIOMA** or **ADENOID CANCER.**—These terms are applied to those forms of epithelial cancer which grow from mucous membranes with columnar (cylindrical) epithelium—*e. g.* the stomach and intestines, and especially the rectum and uterus. In these tumors the epithelial elements are similar to those of the mucous membrane from which they grow. They are cylindrical in shape, and are arranged perpendicularly to the walls of the alveoli in a manner precisely analogous to that of the columnar epithelium on the mucous surface (Fig. 66). The slower

FIG. 66.



Cylindrical Epithelioma: From the colon. × 200, reduced ½.

the growth, the more typical the gland-formation; in rapid growths and recurrences the cells are small, the lumina imperfect. The latter may be filled up, and the growth be indistinguishable from glandular cancer, except by its edge, where a low columnar or cubical form usually persists, but this too may be lost. The growths are of a soft and often gelatinous consistence; they tend strongly to undergo colloid degeneration. These tumors cause secondary growths in the lymphatic glands, and sometimes in the liver, lungs, and bones, which possess the same characters as the primary cancer. The distinction

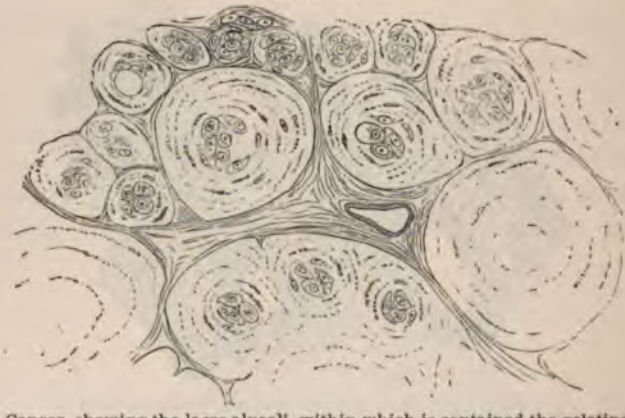
between them and simple adenomata depends upon the invasion of tissue by the cancers.

"Colloid Cancer."

COLLOID or **GELATINIFORM CANCER** is simply one of the preceding forms which has undergone a mucoid or colloid change. Sarcomatous and other non-cancerous growths may undergo this change. (See "Colloid Degeneration.")

The alveolar structure in colloid cancers is very marked. The alveoli have very thin walls; they are large, distinct, and more or less spherical in shape. This large size and distinctness of the alveoli is owing to their distension by products of degeneration. These form gelatinous colloid material, which is glistening, translucent, colorless, or yellowish, and of the consistence of thin mucilage or size-gelatin. In the main it is perfectly structureless; within it, however, are

Fig. 67.



Colloid Cancer, showing the large alveoli, within which is contained the gelatinous colloid material. × 300. (Rindfleisch.)

imbedded a varying number of epithelial cells (Fig. 67). These cells present a peculiar appearance; they are large and spherical in shape, and are distended with drops of the same gelatinous material as that in which they are imbedded. (See Fig. 67.) Many of them display a lamellar surface, their boundary being marked by concentric lines. It would appear that the colloid change commences in the cells, which become gradually destroyed in the process.

In other cases, similar to the naked eye, the cells, with the excep-

tion of slight fatty metamorphosis, are but little affected, and the substance distending the alveoli is more viscid and mucoid in character. This is due to a **mucoid degeneration** (p. 79) of the intercellular substance, rather than to a colloid change commencing in the cells.

Colloid cancer is most frequently met with in the stomach, intestine, ovary, and peritoneum. In the latter case it is either secondary or the growth is a sarcoma.

The Teratomata.

These tumors can only be mentioned. They are congenital, and occur chiefly in the sacral region (coccygeal tumors), the head and neck—points at which double monsters are united—but they may be internal. Many of them are due to the inclusion and imperfect development of one fœtus within another; others to abnormal development of the tissues of one fœtus. They are most complex, and may contain all the tissues of the body up to ganglion-cells more or less confusedly mixed. They may be very large at birth, or may not attract notice till later. Dermoid cysts belong to this group.

CHAPTER XXIV.

CYSTS.

In addition to the new growths already described, there is a large class of formations, many of which cannot be regarded as "tumors" in the strict application of this term. These are the **cysts** or "**cystic tumors.**"

A **cyst** is a cavity containing liquid or pultaceous material which is separated from the surrounding structures by a more or less distinct capsule. It may be a new formation or a pre-existing structure which has become distended by its own secretion or by extravasation into it. Only the former comes within the category of new growths, but for the sake of convenience it will be advisable to consider them both under one head.

There are thus two principal modes by which cysts originate: one, the most frequent, by the gradual accumulation within the cavities of pre-existing structures of substances which are, for the most part, products of their own formation, being in some cases a secretion and in

others a cell-growth; the other, by the independent formation of a cyst in the tissues.

The accumulation of secretions and of other products within pre-existing cavities may be effected in the three following ways:

1st. By the retention of the normal secretion owing to the closure of the excretory ducts, as so often occurs in sebaceous glands.

2d. By excessive secretion, the cavity being unprovided with an excretory duct, as in the distension of bursæ.

3d. By the extravasation of blood into the cavity, as in hæmatocele.

The independent formation of a cyst may take place—

1st. By the softening and liquefaction of the tissues in some particular part, owing to mucoid or fatty changes. The tissues around the softened matters become condensed, and ultimately form a kind of cyst-wall.

2d. By the collection of fluid in certain spaces of connective tissue, and their subsequent enlargement and fusion. The surrounding tissue becomes condensed, and forms a cyst-wall; and this may in some cases become lined with flattened connective-tissue cells (endothelium).

3d. By the formation of a cyst-wall around foreign bodies, parasites, or extravasated blood: the wall consists of fibrous tissue and is the result of a chronic inflammation.

STRUCTURE.—The **wall** of a cyst will vary in its nature according as it is that of a pre-existing or a newly-formed cavity. In the former case it will possess an epithelial lining which will present the same characters as that of the gland, serous membrane, or other structure from which the cyst originated. If the cyst is of independent formation, there is no endothelial lining to the fibrous capsule, but one may develop later, as in false bursæ. The cyst-wall is sometimes firmly connected with the adjacent parts, so that it can only with difficulty be separated; in other cases the union is much less intimate. Instead of being a distinct structure, it may be simply the surrounding tissue which has become dense and fibrous in character.

The **contents** of cysts are very various, and may serve as a basis for their classification. In the retention-cysts they will vary with the nature of the normal secretion: serum, sebaceous matter, saliva, milk, seminal fluid, and other substances are thus found in these cysts, more or less altered in character from being retained in a closed cavity. In the exudation-cysts serum is the most frequent constituent; and in

extravasation-cysts, blood. In those cysts which originate from the softening and breaking down of tissue the contents are the products of retrogressive tissue-metamorphosis, and usually consist largely of mucin, fatty matters, and serum.

Cysts may be **simple** or **compound.** A simple cyst consists of a single loculus. A compound or multilocular cyst is one consisting of numerous loculi, which either communicate with one another or remain isolated. Another variety of compound cyst consists of a cyst with endogenous growths, the larger cyst having others growing in its walls. A compound cyst may become a simple one by the destruction of its walls.

Cysts are frequently associated with other growths, hence the terms "cystic sarcoma," "cystic cancer," etc. It is especially in those growths which originate in glandular structures, as in the mamma, testicle, and ovary, that this combination is met with. The cystic development may almost entirely obliterate the structure of the tumor in which it takes place, so that ultimately the latter becomes converted into a combination of cysts. In other cases large papillary masses of the tumor grow into the cystic cavities ("compound proliferous cysts"). Considerable difficulty is thus not unfrequently caused in determining the nature of the original growth.

SECONDARY CHANGES.—These may take place in the wall of the cyst or in its contents. The cyst-wall itself may become the seat of new growths, and produce secondary cysts, villous, glandular, and other structures: this occurs in many compound ovarian cysts. It may also be the seat of an inflammatory process which terminates in suppuration and granulation, and by this means the cyst frequently becomes obliterated, its contents being either absorbed or discharged externally, and the cavity closing by granulation. Calcification and ossification of the wall may also occur. The contents of cysts undergo various changes, owing to their retention in a closed cavity. The secretions become altered in character, thickened, and viscid. Epithelial elements undergo fatty changes, and so give rise to cholesterin crystals. Calcification of the contents is also common.

CLASSIFICATION.—Cysts may be most conveniently classified according to their mode of origin, thus:

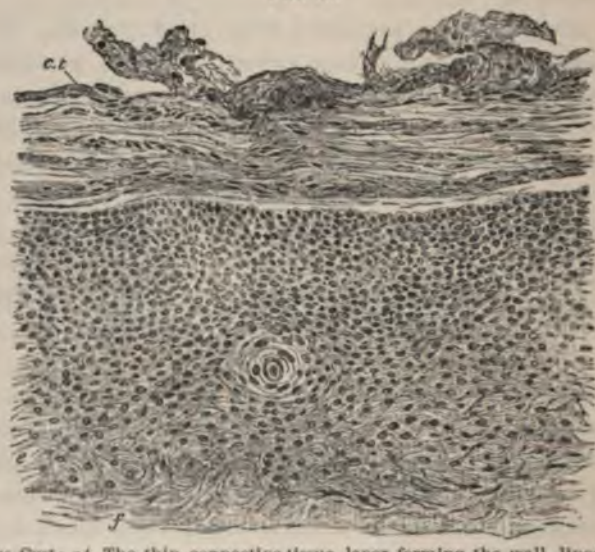
Classification of Cysts.

I. *Cysts formed by the accumulation of substances within the cavi of pre-existing structures.*

A. Retention-Cysts. Cysts resulting from the retention of nor secretions. These include—

a. Sebaceous Cysts. These are formed by the retention of se tions in the sebaceous glands. They possess a v thin connective-tissue wall lined by stratified epitheli

Fig. 68.



Sebaceous Cyst: *c.t.* The thin connective-tissue layer forming the wall, lined by a t layer of epithelium. The outer cells of this are somewhat cubical; then, passing inward, become flattened, and finally they enlarge considerably, become fatty, and rather sudd cease to stain. They are succeeded by fatty débris (*f*), compressed so as to have a fib aspect.

(Fig.68.) They contain a mass of fatty epithelium its products, débris, cholesterin, etc.

β. Mucous Cysts. These are formed by the retention of se tions in the glands of mucous membranes.

γ. Cysts from the retention of secretions in other parts, incl ing ranula, when due to occlusion of the salivary du encysted hydrocele, from occlusion of the tubuli tes cysts in the mammary gland, from obstruction of lacteal ducts; simple and some compound cysts of

ovary, from dilatation of the Graafian follicles; and simple cysts of the liver and kidneys.

B. EXUDATION-CYSTS. Cysts resulting from excessive secretion in cavities unprovided with an excretory duct. These include bursæ, ganglia, hydroceles, meningoceles, cystic bronchocele, and many cysts in the broad ligament.

C. EXTRAVASATION-CYSTS. Cysts resulting from extravasation into closed cavities. These include hæmatocele and some other forms of sanguineous cysts.

II. *Cysts of independent origin.*

A. CYSTS FROM SOFTENING OF TISSUES. These are especially common in new formations, as in chondroma, lipoma, sarcoma, etc.

B. CYSTS FROM EXTRAVASATION INTO SOLID TISSUES—*e. g.* brain, soft new-growths.

FIG. 69.

Dermoid Cyst of the Ovary, showing all the structures of true skin except sweat-glands—viz. epithelium, rudimentary papillæ, fibrous tissue or cutis vera, hair-follicles, large sebaceous glands. × 18.

C. CYSTS FROM EXPANSION AND FUSION OF SPACES IN CONNECTIVE TISSUE. These include—

a. Bursæ, originating from irritation and exudation into the tissues.

β. Serous cysts in the neck, hygroma (often congenital).

γ. Many compound ovarian cysts.

D. Cysts formed around Foreign Bodies, Extravasated Blood, and Parasites.

E. Congenital Cysts. Many hygromata, dermoid cysts. Sometimes these appear to be the remains of blighted ova, but usually they are due to inclusion of a piece of epiblast. Their wall has more or less perfectly the structure of skin (Fig. 69); they contain fatty matters, a coil of long, fair hair, and rarely teeth, bones, etc.

CHAPTER XXV.

CHANGES IN THE BLOOD AND CIRCULATION.

INTRODUCTION.—The vascular system is a closed system of tubes, capable of varying in capacity, and having inserted at one point a muscular organ, so constructed that it can receive on one side venous blood at a minus pressure, and send out on the other arterial blood with force sufficient to carry it right through the systemic or pulmonary circulation. The heart-force is aided by the pressure of contracting muscles upon valved veins and by thoracic aspiration. Each time an artery branches the sectional area of the arterial system is increased; so also is its extent of surface. But in both these respects by far the greatest increase takes place in the region of arterioles and capillaries. Increase of surface means increase of friction, and enlargement of the area upon which a given force has to act must also diminish the effect of that force. Consequently, the blood-stream becomes suddenly slowed in the arterioles and capillaries. The arterioles vary in diameter much more than do larger arteries, for they contain proportionately much more muscle. The resistance in the arterioles, therefore, varies enormously under diverse influences, but the diameters of capillaries seem to change only in response to variations in pressure. The sectional area of the venous system, on the other hand, diminishes from the capillaries to the heart, and the rate of flow increases proportionately as the region in which thoracic aspiration acts is approached.

Gravity must not be regarded as a cause of circulation: what the blood loses or gains on its way from the heart will be exactly balanced during its return to the heart. But, though gravity has noth-

ing to do with the driving force, it increases the *pressure* in vessels.

This is best shown by a U-tube: the pressure varies directly as the height of the columns in the limbs, but no movement occurs unless a driving force is added.

The quantity of blood in the body may be regarded as constant in normal states.

Circulatory disturbances may be produced in many ways. The heart may act so feebly or be so damaged structurally (valve-disease) that too little blood enters the arteries at each stroke, and generally at a pressure less than normal. As a result, the arterial supply of all parts is diminished, blood lags in the veins, and a less quantity than normal enters the heart during each diastole. More rarely, the heart may act so forcibly as to rupture delicate or diseased vessels.

Supposing the heart to act normally, it is obvious that with a constant blood-mass the total capacity of the vascular system must be kept within certain limits. It may easily dilate so as to contain all the blood (the abnormal veins alone would do this after section of the splanchnics), when the heart would receive none and circulation would cease. Or the arterioles may contract so as to more or less completely stop circulation and drive all the blood into the veins. Between these extremes there is a state of the vascular system, corresponding to any given heart-force, which is most favorable for the circulation: this is normal tonus. It is the province of the vaso-motor system to maintain this relation between heart and vessels. Enlargement of the vascular system, whether due to general or local diminution of vascular tonus, slows the circulation; diminution of the capacity of the system, in moderation, quickens it. In cases of local increase of tonus the blood which the more or less anæmic parts should contain is thrown into the system at large, and raises the blood-pressure until the vaso-motor system causes other vessels to dilate compensatorily, so as to receive both their own blood and that of the contracted vascular area. Such compensation is effected very rapidly, the general rise of pressure after ligature of a main artery being quite transient (Roy). Parts supplied by vessels so dilated are said to be in a state of "compensatory hyperæmia." If, on the other hand, a vascular area dilates, the vaso-motor system generally causes other areas to contract, so as to preserve the capacity of the vessels about the same, and thus keep up the pressure; that is to

say, other parts become anæmic to provide the hyperæmic one with blood. This state might be called "compensatory anæmia."

Local Anæmia.

Strictly, "anæmia" means bloodless, but it is rarely used alone in this sense. Unqualified, it signifies a morbid state in which the blood, as a whole, is deficient in hæmoglobin; but **local** anæmia means that there is too little blood in a part owing to diminished arterial supply. It may be partial or complete.

CAUSES.—The causes of diminished arterial supply to a part are all those conditions which either narrow or completely close the lumen of the supplying artery. The lumen of an artery may be diminished by disease of its walls—atheroma, calcification, or syphilitic thickening, or by pressure exercised upon it from without, as by new growths, stricturing scars, inflammatory exudations, and mechanical effusions, especially in unyielding tissues, as bones or tendon-sheaths. Complete closure of the vessel may result from some of the foregoing conditions, or, more commonly, from thrombosis, embolism, or ligature. In some cases the supply of blood is diminished by an increase in the natural resistance from irritation of the vaso-motor nerve. This occurs as the result of a low temperature in some neuralgic and other nervous affections, and from the action of certain substances, such as ergot of rye, opium, etc. Anæmia may occur also from hyperæmia of other parts—*e. g.* of the brain and skin in congestion of the abdominal viscera; and from the presence of too little blood in the system, as after hemorrhage, when the distal parts suffer most.

RESULTS.—A part with diminished arterial supply is usually paler, less tense, and of a lower temperature than natural. Its nutrition and function also are impaired, so that it may undergo fatty degeneration, atrophy, or die. These results were exemplified in the chapters on Atrophy, Fatty Degeneration, and Necrosis.

Obstruction of a large artery causes rise of pressure (transient under healthy conditions, p. 201) everywhere except in its own area; and this increased pressure endangers the safety of delicate or diseased vessels until the extra blood thrown into the suddenly curtailed vascular system is accomplished in some way. The heightened pres-

sure affects the vaso-motor centre, and this speedily produces sufficient dilatation of vessels to restore the normal state. But the vessels which dilate most markedly and persistently are those going to the anæmic part and anastomosing with branches from the trunk beyond the obstruction: this is probably owing to some obscure vaso-motor mechanism, excited, probably, by the anæmia. These "collateral" vessels become larger, longer (tortuous), and thicker until the circulation in the part has again become normal—*i. e.* **collateral** circulation is established. At first, probably all vessels having anastomoses with the obstructed one dilate; but those which enlarge permanently are almost invariably branches on the same side as the obstruction—*e. g. right* inferior thyroid and vertebral after ligature of *right* carotid. The primary anæmia, the blush and heightened temperature of vascular dilatation and return to the normal, can be seen in limbs after ligature of main vessels.

In certain organs, however, there is either but one supplying artery, or others entering it are insignificant; further in the spleen, kidneys, lungs, brain, and retina, the branches of the main vessels communicate only by capillaries: such arteries are called **terminal** by Cohnheim. Here collateral circulation cannot be established, and obstruction leads either to immediate or speedy arrest of the circulation through the part, with or without "**infarction**" (p. 230); and its tissues consequently die and degenerate fattily ("**necrobiosis**"). The results of obstruction of terminal arteries will be fully considered under Embolism.

HYPERÆMIA.

Hyperæmia, or congestion, is excess of blood in the more or less dilated vessels of a part. It may be **active** or **arterial** and **mechanical** or **venous**. These two varieties must be considered separately.

Active or Arterial Hyperæmia.

Active hyperæmia means excess of arterial blood in a part, with, in most cases, acceleration of flow.

CAUSES.—The immediate cause of active hyperæmia is in all cases **diminished arterial resistance.**

Diminished arterial resistance may be produced pathologically—

1st. **By certain agencies which have a weakening or paralyzing effect upon the involuntary muscle of vessel-walls.** Fatigue from previous prolonged contraction has this effect, as seen in the hyperæmia of the hands which follows snowballing. Warmth, too, is generally placed under this heading. Injuries of all kinds, when not acting suddenly and with extreme severity, produce a reflex hyperæmia by their influence on sensory nerves before the true inflammatory dilatation, which must be included in the next group of cases, sets in. But the dilatation characteristic of inflammation is due to direct damage of the vessel-wall, and therefore falls under this heading; and so long as it is more than sufficient to counterbalance the increased resistance which always accompanies it (see "Inflammation"), the quantity of blood passing through the part will be greater than normal—*i. e.* the part is hyperæmic. The sudden removal of pressure is another cause of hyperæmia, proved by the congestion of the abdominal vessels which results on the removal of much ascitic fluid or of a large ovarian tumor; by the bleeding which occurs when a pleura is more or less completely emptied by aspiration or strong syphon-action; and by the hemorrhage which often follows the complete emptying of a chronically distended bladder. The muscle of the vessels, accustomed to much support, has lost power; so, when the support is suddenly removed, the vessels dilate fully and small ones perhaps rupture.

2d. **By the removal, either directly or reflexly—*i. e.* by inhibition—of the vaso-tonic action of the sympathetic.** Examples of the *direct* process are—the active congestion which follows pressure upon the sympathetic, as in the neck by an aneurism or section of vaso-motor nerves in any part of their course, from the centre in the medulla down the cord into spinal nerves or sympathetic plexuses. Thus, unilateral congestion results from diseases and experimental sections of half the spinal cord. Certain drugs, taken internally, are believed to temporarily and directly paralyze the vaso-tonic nerves—*e. g.* nitrite of amyl, alcohol, tobacco.

The *reflex* process is generally due to stimulation of sensory nerves, the diminution in tonus thus produced being more or less accurately confined to the region supplied by the nerve. Friction and slight irritants in the early stages of their action produce hyperæmia in this way (see above). It seems that vascular dilatation of deep organs may be produced reflexly by the application of stupes to the skin over them.

Anæmia of any large part—as of a limb compressed by Esmarch's bandage, or of the skin from cold—necessarily causes hyperæmia of other parts—**compensatory hyperæmia.** But all parts do not suffer equally, as they would were the hyperæmia the result simply of increased arterial pressure: certain vessels, as the great abdominal veins, dilate, showing that the vaso-motor system arranges for the accommodation of the surplus blood by producing local diminutions of vascular resistance. After extirpation of one kidney its share of blood passes mainly to the other.

3d. **By excitation of vaso-dilator nerves,** such as the chorda tympani. Nothing is certainly known of this as a cause of hyperæmia; but the hyperæmia associated with facial neuralgia and that of the thyroid in exophthalmic goitre have been referred to vaso-dilator neuroses and also to inhibition of vaso-tonic nerves.

RESULTS.—The results of active hyperæmia are principally such as might be expected from increase in the amount of arterial blood and in the rapidity of its flow in any particular organ or tissue. The symptoms in a superficial part are—increased redness and pulsation, a sensation of throbbing being often experienced by the patient; some increase in bulk; marked elevation of temperature, amounting in a distant part, like the foot, to several degrees. If the hyperæmia be of long duration or frequently repeated, the small arteries become permanently enlarged, their walls gradually thicken, and the epithelium and connective tissues of the part increase, as may be seen in the papillary thickening round a callous ulcer of the leg and the occasional spread of ossification into the granulation-tissue from the tibia. Hypertrophy of other tissues also is a frequent result if they be called upon to functionate. (See "Hypertrophy.") Function is increased, except in organs, as the submaxillary gland, which functionate only in response to nervous stimulation. Thus, in hyperæmia of the nervous centres we see great excitability, paræsthesiæ of sight and hearing, convulsions, etc. In glands whose relation to the nervous system is not very close, as the kidneys, secretion is increased, the urine being watery and sometimes albuminous.

Mechanical or Venous Hyperæmia.

In venous hyperæmia the excess of blood is in the veins and capillaries, and the flow, instead of being accelerated, is retarded. This

is so frequently produced by some obvious mechanical obstacle to the return of blood through the veins that it is often called **mechanical** hyperæmia. The congestion of a finger, produced by a moderately tight band round it, may be taken as the type of such cases.

CAUSES.—Anything which weakens the forces carrying on the venous circulation or which opposes unusual resistance to this circulation—anything which lowers the blood-pressure and slows the stream—must tend to produce venous hyperæmia. It is evident from the remarks introductory to this section that such causes may exist in any part of the vascular system—heart, arteries, capillaries, or veins—some having a local, others a general effect. They may be ranged under two headings—(1) those which **diminish** *vis a tergo*, or force with which the blood should be driven through the veins; and (2) those which **directly impede the return of blood by the veins.**

1. Diminished cardiac power is chief in the first group, and one of the most important causes of mechanical hyperæmia. The motor-power of the heart becomes impaired in many of the chronic exhausting diseases, also in the acute febrile diseases, as in typhus and typhoid fever, and in those degenerations of its structure which lead to dilatation of its cavities. In whichever of these ways the *vis a tergo* is diminished, that diminished fulness of the arteries and over-fulness of the veins which is so familiar clinically as the result of cardiac failure will be produced. If this condition be of long duration, there is necessarily so much interference with the oxygenation of the blood, with the functions of the blood-forming organs, and with the processes of digestion and assimilation that the blood itself becomes deteriorated, and thus by its lagging in every tissue nutrition in general suffers.

In the arteries the driving force may be weakened by obstruction, total or partial, of an arterial trunk from any cause, or by uncompensated dilatation (p. 201) which is likely to arise from simple atony or from those general fatty, atheromatous, or fibroid changes of the arterial wall so common in advanced life.

Obstruction to the circulation in capillaries arises mainly from pressure of inflammatory effusions, dropsy, etc. on capillary areas.

With regard to veins, the circulation will be slowed by absence of muscular contractions, especially in the lower extremity, or such dilatation as produces incompetence of valves, and thus renders muscular action useless as an aid to circulation; also by anything which dimin-

ishes the elastic force with which the lung tends to draw away from the pleural wall, and thus lessens thoracic aspiration. Forcible expiration will replace the normal minus-pressure within the thorax by a plus-pressure, and thus playing wind instruments impedes entry of blood from veins into the heart. Emphysema, effusion of air or fluid into the pleuræ, and large new growths of the lung act similarly. These causes might fairly rank under the second heading.

When, by the above conditions, variously combined, the circulation is much retarded, **hypostatic congestions** of the posterior edges and bases of the lungs, of the skin over the sacrum, and of other parts kept constantly dependent occur. Slowing of the circulation causes the veins of distant parts to become especially full. If such a part be also dependent, the pressure (not the driving force) in its vessels is increased by gravity in proportion to the vertical distance from the highest point of the body, in any given position, to the part in question (p. 200); and if the patient is so weak as to be unable to change his position this high pressure is constantly maintained, dilating veins and capillaries more or less fully, and greatly increasing the tendency to leakage through the malnourished vessels. Thus the part is redder than normal and œdematous, also softer. The base of the lung seems but a short way from the heart; it is, however, the point in the pulmonary circulation farthest from the right ventricle, which is weaker than the left in proportion as the resistance which it has to overcome is less. Moreover, in bedridden patients breathing is often very shallow, and the effect of expiration in driving blood on to the left auricle is much diminished. (See "Hypostatic Pneumonia.") That dropsy from hydræmia or heart disease begins in the legs of people who are walking about is also due largely to gravity.

2. Direct impediments to the return of blood by the veins are numerous. Congestion of the chylopoietic viscera from compression of the portal capillaries in cirrhosis of the liver; of the lung in mitral constriction and regurgitation; of the systemic circulation in insufficiency of the tricuspid valve; and of the lower extremities from the pressure of the gravid uterus on the iliac veins, are a few of the numerous familiar examples of "mechanical hyperæmia."

RESULTS.—Whether there be a direct impediment to the return of blood by the veins or a failure in the forces of circulation, the veins and capillaries dilate, and the blood accumulates in them and moves with diminished velocity. The subsequent changes will depend upon

the degree of obstruction to the venous return and upon the arter pressure; in other words, upon the injury sustained by the vess walls from impaired nutrition, and upon the increase of pressure the veins and capillaries. The most important of these changes are the exudation of serum, the escape of red blood-corpuscles, hemorrhag fibroid induration, thrombosis, and necrosis.

1. **Exudation of Serum** is the earliest and one of the most impo ant results of mechanical hyperæmia. The influence of increased pr sure upon the amount of transudation is shown experimentally thu Tie the main vein of the ear of a rabbit on each side, and divide t sympathetic in the neck on one side; the transudation of serum in the ear of that side on which the nerve is divided will be very co siderable, whilst on the other it will be slight or entirely wantin The serum transudes from the capillaries and small veins, and r from the small arteries, and differs from plasma in being of lower sp cific gravity, in containing less albumen, and in having very lit tendency to coagulate, which is probably due to the small number white corpuscles present in it. Red corpuscles may be present small or large numbers, varying directly with the amount of obstru tion. The greater the pressure and the more the nutrition of the w suffers, the more nearly does the transuded liquid resemble the liqu sanguinis, and the greater the amount of albumen which it contain If the pressure be very great, it may yield a fibrinous coagulum.

The increased absorption by lymphatics which follows increas transudation from the blood-vessels may be sufficient to prevent a accumulation of serum in the part, as is the case, for example, in t ear of the rabbit, where the main vein is obliterated, but the arteri are not dilated. (See above.) Where the lymphatic absorption, ho ever, is insufficient to remove the transuded liquid, this accumula and gives rise to **œdema** or dropsical effusion. The amount of tra udation will be influenced by the anatomical characters of the tiss being most in those parts in which the blood-vessels are least su ported, as in the subcutaneous tissue, and in tissues which present free surface, as serous and mucous membranes. A lax and tonel condition of the vessels also will favor transudation.

2. **Escape of Red Blood-corpuscles occurs** when obstructi to the venous return is great; they transude with serum from t veins and capillaries. This, in mechanical hyperæmia, was discover by Cohnheim, who observed it in the web or tongue of the frog aft ligature of the main vein. The red corpuscles accumulate in incre

ing numbers in the veins and capillaries, the blood-stream in these vessels completely stagnates, the red corpuscles become so closely packed that their individual outlines are scarcely distinguishable, the coherent mass oscillates to and fro with the arterial pulsation, and then suddenly some of the red corpuscles penetrate the walls of the small veins and capillaries and escape into the surrounding tissue. This occurs without rupture of the vessel, and if the ligature be removed the blood again circulates in a perfectly normal manner. The corpuscles appear to be squeezed through the capillary walls as the result of the pressure, and rarely escape in great numbers. Perhaps they pass through the stomata which Recklinghausen has shown to exist between the endothelial elements; but as plasma could easily pass through openings large enough for a red corpuscle, and as the transudation-fluid differs markedly from plasma, Cohnheim considers that the existence of these stomata is unnecessary to account for the escape of corpuscles.

3. **Hemorrhage** is another result of mechanical hyperæmia, which usually occurs only when the obstruction to the venous current is very great. It is probable, too, that the nutrition of vessels and tissues has suffered from long congestion; for very heavy strains may be put upon healthy vessels without their giving way. Those vessels which are the least supported are the first to give way. Hemorrhage into the stomach in cirrhosis of the liver and into the lung in mitral disease are familiar examples.

4. **Fibroid Induration** is due to a gradual increase in the connective tissue round the blood-vessels, and is one of the most important results of long-continued mechanical hyperæmia. The interstitial growth leads to atrophy of the higher structures, and thus to impairment of the functions of the organ. In the stomach it produces atrophy of the glandular structures; in the kidney, compression of the urine tubes; in the liver, obstruction to the portal circulation; in the heart, diminution in motor-power. The alterations which this change produces in the physical characters of the organs—viz. induration associated with abnormal redness, due to the excess of blood or pigmentation from hæmatoidin—are exceedingly characteristic.

5. **Thrombosis**, as a result of mechanical obstruction, will be described in the following chapter.

6. **Necrosis** occurs from mechanical hyperæmia only when the obstruction is very general and complete. It has been already described (pp. 38, 41).

In addition to the foregoing results, long-continued mechanical hyperæmia leads to impairment of vitality and function. The tissues gradually undergo retrogressive changes and atrophy, although from the amount of serosity and blood which they contain their size and absolute weight may be increased. Their temperature becomes lowered. This form of hyperæmia has no tendency to cause multiplication of tissues other than the connective (fibroid induration) and the epithelial, as seen in catarrhs of mucous membranes.

POST-MORTEM EVIDENCES OF HYPERÆMIA.—Frequently, parts which were hyperæmic during life, especially actively so, show no signs of it after death; for if the blood does not coagulate rapidly contraction of the arteries or of the elastic capsules of an organ (*e. g.* kidney) forces it on into the veins, thus rendering the recognition of arterial or capillary hyperæmia impossible. Further, under the influence of gravity alone fluid blood will tend to run to the more dependent parts and thus a hyperæmic organ—whether actively or passively so—may be emptied of blood and rendered pale.

But dependent parts, on the other hand—the posterior portions of the lungs, the lowest coils of intestine, the skin on the posterior surface in dorsal decubitus—which may have been healthy during life, now become full of dark blood, and it is often difficult to say how much of the congestion of the base of a lung is ante-mortem and how much post-mortem.

A further source of error exists in the post-mortem staining of parts, especially of the endocardium and linings of great vessels and of the tissues round veins, met with particularly in septicæmia. The redness in these cases is uniform, and no magnification will show that it is due to vessels distended with blood. A simple lens will generally show the capillary nature even of an apparently uniform red from hyperæmia.

When considerable veins are hyperæmic the injection is said to be "ramiform," from their branching form and dark-blue color. Injection may appear "punctiform" in the intestine and skin (villi and papillæ) and in the kidney, in which the Malpighian corpuscles stand out prominently. Minute punctiform hemorrhages must not be confused with such cases.

Pigmentation (slate-gray, black, or brown) from altered hæmoglobin of escaped corpuscles generally remains after chronic hyperæmia, as is often well seen in the stomach and intestines after portal congestions and chronic catarrhs in the bladder and in the lungs.

Mechanical Hyperæmia of the Liver.

Nutmeg Liver.—Long-continued mechanical hyperæmia of the liver gives rise to the condition known as nutmeg liver, which so frequently results from cardiac incompetence. The change is characterized by a large accumulation of blood in the hepatic ("central") veins, which dilate and thicken; by atrophy of the hepatic cells in the central portions of the acini; and by increase of the interlobular connective tissue. The impediment to the return of blood by the hepatic vein leads to pressure-atrophy of the cells in the central portions of the acini and to the formation of granular pigment, so that, when examined microscopically, these portions of the acini are seen to consist of broken-down cells and granules of pigment (Fig. 70). The veins here are found much dilated and filled with red blood-corpuscles (Fig. 71). Their walls are thickened, and there often appears to be also more or less thickening of the intercellular network which immediately surrounds the central vein. Owing to the thickening of the central vein and of the adjacent intercellular network, and to the

Fig. 70.

Nutmeg Liver: Destruction of the liver-cells and pigmentation of the central portions of the acinus; new growth of connective tissue at the periphery. V. Hepatic vein. P. Portal canal. × 50. (When more highly magnified numerous nuclei are seen in the peripheral connective tissue.)

Fig. 71.

Nutmeg Liver: Portion of Fig. 70, around central hepatic vein (V); more highly magnified, showing the thickening of the veins and the accumulation of red blood-corpuscles within them. × 400.

destruction of the liver-cells, the most central portions of the acini, in advanced stages of the disease, may present a fibrous appearance. At the peripheral parts of the acini the new interlobular growth is seen insinuating itself between

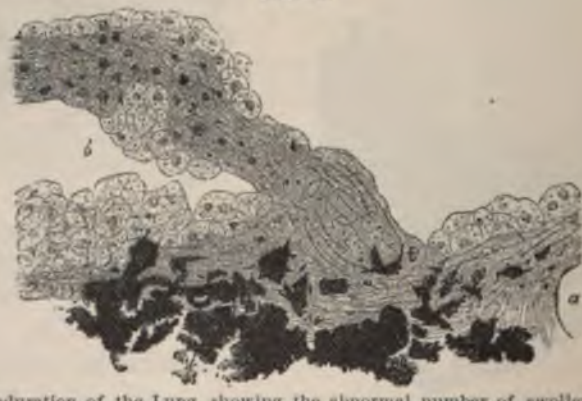
the almost unaltered liver-cells. This new interlobular growth is usually distinctly nucleated, but, for the most part, less so than that met with in cirrhosis. Its cellular character has been insisted upon especially by Dr. Wickham Legg.

In the earlier stages of this affection the liver is smooth, and often considerably increased in size from the large amount of blood which it contains. On section it presents a peculiar mottled appearance, the centre of the lobules being of a dark-red color, whilst the peripheral portions are of a yellowish-white. This latter appearance is often increased by fatty infiltration of the peripheral liver-cells. Ultimately, the organ may undergo a gradual diminution in size, becoming more or less irregular on the surface. This is due to atrophy of the central cells of the lobules, partly from pressure of the dilated central veins and malnutrition, and partly from the pressure of the contracting interlobular growth. The interlobular growth tends to cause obstruction to the portal circulation, as in cirrhosis.

Mechanical Hyperæmia of the Lungs.

In the lungs, long-continued mechanical hyperæmia produces that peculiar induration and pigmentation which is known as **Brown**

Fig. 72.



Brown Induration of the Lung, showing the abnormal number of swollen pigmented epithelial cells covering the alveolar walls, the increase of connective tissue around the blood-vessels, *a*, and the large quantity of pigment. *b*. The alveolar cavity. × 200.

Induration. This most frequently results from stenosis and insufficiency of the mitral orifice. The alterations produced in the pulmonary texture consist, in the first place, of elongation and dilatation of the

pulmonary capillaries, so that even in uninjected preparations the alveolar walls appear abnormally tortuous. The epithelial cells lining the alveoli become swollen, probably multiply, and are seen in large numbers, filled with dark-brown pigment, covering the alveolar walls (Fig. 72). They frequently accumulate within the alveolar cavities. These changes are followed by an increase in the interlobular connective tissue, by the formation of large quantities of brownish-black pigment, and often by a thickening of the alveolar walls. Sometimes the pulmonary capillaries rupture, and blood is extravasated into the lung tissue.

Lungs in which these changes are at all advanced present a more or less uniform brownish-red tint, mottled with brown or blackish-colored specks and streaks. They are heavier and tougher than natural, less crepitant, and upon squeezing them the pulmonary tissue is found to be denser and thicker than that of a healthy lung.

CHAPTER XXVI.

THROMBOSIS.

THROMBOSIS is a coagulation of the blood within the vessels during life. The product is called a **thrombus**, in opposition to a **coagulum** or **clot**—the result of post-mortem coagulation. It may occur in the heart, arteries, capillaries, or veins, but is most common by far in the veins.

PHYSIOLOGY OF COAGULATION.—There is much difference of opinion upon most of the essential points in the coagulation of the blood. According to Schmidt, coagulation consisted in the union of two albuminoid bodies—**fibrinogen** and **fibrino-plastin**—under the influence of a third, called the "fibrin-ferment," though no true ferment-action is attributed to it. Fibrinogen exists in normal plasma; fibrino-plastin and fibrin-ferment are found in serum, having arisen, it is thought, also from leucocytes, over 70 per cent. of which have been described as breaking up on the escape of blood from the body. As disintegration of leucocytes is going on constantly, a small quantity of the ferment was said to be normally present in circulating blood, inhibited from acting by the vessel-wall; but blood received

from an artery into absolute alcohol has been proved to contain none. Next, Hammarsten showed that fibrino-plastin was unnecessary to coagulation, a normal clot being formed when the fibrin-ferment acted upon fibrinogen alone. Rauschenbach found that yeast added to cooled plasma induced coagulation just as the fibrin-ferment did, although yeast yields no such ferment. Wooldridge has explained this action of yeast by pointing out that it, like leucocytes, is rich in **lecithin**, a body which his experiments have shown powerfully to induce coagulation. Wooldridge further states that Schmidt's fibrin-ferment does not exist in normal plasma, and that it may make its appearance in plasma from which all cells have been removed by the centrifugal machine; he believes it to arise from some as yet undetermined constituent of the plasma itself, to vary in amount with the energy of coagulation, but not to be an essential element in coagulation.

Lastly, Wooldridge states that fibrin is due to the union of two bodies, which he calls "fibrinogen A," corresponding to the body called "fibrinogen" above, and "fibrinogen B," which he has obtained as a precipitate from plasma, the precipitate consisting of bodies indistinguishable from "microcytes" or "blood-plaques."

Quite recently Haycroft and Carlier have expressed themselves as opposed to the view that a large number of leucocytes disappear when blood is drawn from the body.

EXCITING CAUSES OF COAGULATION.—The most striking points are that, speaking generally, blood circulating in living vessels remains fluid, but when drawn from the body it coagulates, and that when coagulation of circulating blood occurs it is usually upon some obviously diseased surface or in a part in which the blood-stream has been much retarded. From these facts it has been inferred that the healthy vessel-wall exercised an inhibitory influence upon the blood, preventing the changes (whatever they may be) which lead to the formation of fibrin. It is probably more correct to say, with Sir J. Lister, that blood within normal vessels does not tend to coagulate, the vessel-wall being, so to speak, neutral or passive so long as it is living and healthy. In this light the normal vessel-wall may be compared to the greasy and viscous substances, like vaseline, paraffin, and castor oil, in which blood may long be kept fluid, yet ready to coagulate normally when brought into contact with solid matter (Haycroft and Carlier). Contact with ordinary solid matter, on the other hand,

induces coagulation more or less quickly: when drawn into a basin, blood usually clots in from three to eight minutes, but Lister saw blood remain fluid for a long time in the angle between an amputated sheep's foot and the skin raised in a flap from it; and extravasations about simple fractures and into body-cavities are often long in coagulating, though they vary much in this respect. A rough surface always acts more powerfully than a smooth.

With regard to the integrity of the vessel-wall, it is necessary only that the endothelium should be sound; fatty and calcareous changes of the *middle* coat do not cause coagulation, whilst atheromatous ulcers, foreign bodies, and nodules of new growths—all bare of endothelium—do; moreover, severe injury of capillaries, which possess only endothelium, causes thrombosis in them.

Prolonged contact with an abnormal vessel-wall will of course favor coagulation, as is well seen in the cure of aneurisms. But **retarded flow** was regarded as an exciting cause of coagulation in apparently normal vessels; and so it is, indirectly, for impaired circulation in a part means damage to its tissues—to its vascular endothelium among others. If the endothelium is kept fairly nourished in spite of stagnation within the vessel, the stagnant blood will not coagulate. Blood within a tied-off turtle's heart does not coagulate till the heart dies. The time before coagulation occurs in the jugular vein of a mammal is longer in proportion to the care with which it is laid bare and the ligatures are applied; and if this operation be done antiseptically coagulation does not occur at all. Retardation, and even stagnation, of flow must therefore be regarded as, at most, but an indirect cause of thrombosis, though it is always a favoring circumstance.

Abnormality or removal of endothelium is therefore the essential condition, and we must next consider and group its many causes:

1. **Injuries and diseases** which destroy or greatly injure the endothelium. The most important, because the most frequent, of these are—section and rupture of vessels, in which thrombosis is the means by which hemorrhage is temporarily checked; and ligature, torsion, cautery, etc. the means by which surgeons temporarily arrest hemorrhage which the natural processes are insufficient to stop. All of these, obviously, cause great injury to the vessel-wall. Other examples of injury are afforded by the action of chemical caustics.

In the heart inflammation of the endocardium causes destruction of its endothelium and the growth of granulation-tissue from the opposed surfaces of valves or elsewhere; coagulation is frequent upon these

vegetations. (See "Endocarditis.") In the vessels, atheromatous ulcers, bare calcareous plates, syphilitic inflammation, and changes due to extension to veins or arteries of spreading inflammations may induce thrombosis similarly. Inflammation was formerly regarded as the main, if not the only, cause of thrombosis; hence thrombosis in veins is frequently termed "phlebitis" even at the present day. Inflammation of veins, as already stated, is certainly rare as a *primary* condition, but it may be due to extension, and not unfrequently *results from* the formation of a thrombus.

The thrombosis which occurs as an occasional complication of acute specific fevers is explained by the observation of Ponfick that in these diseases desquamation of endothelium may occur over large areas of vessels.

2. **The presence in the vascular system of substances not covered by endothelium.** Needles, horsehair, or wire introduced into the sac of an aneurism induce clotting upon themselves, as also do already existing clots (thrombus or embolus), parasites which have penetrated vessels, and new growths which project into the interior of veins.

3. **Imperfect blood-supply of a part, causing disease of the vessel-walls by imperfect nutrition.** This is a most important group, in which slowing of the circulation is the indirect cause. A tendency to stagnation of blood may be due to many causes (p. 208), of which the most important are cardiac weakness, general diminution of vascular tonus, and dilatation (varix) of veins. All these may well be combined in one case to retard the circulation, and thus to produce an abnormal vessel-wall and prolonged contact of the same blood with it. They are the conditions which give rise to the "marasmic clots" of Virchow. These form in the most dependent veins—*e. g.* those of the lower limb, pelvis, or back—and in those parts of the heart in which blood tends earliest to remain when the organ does not completely empty itself; viz. the auricular appendices, the apices of the ventricles, and between the trabeculæ. In veins these clots begin just behind the flaps of valves. The force of the venous current being so slight or the resistance to it being so great that it no longer completely opens the valves, the blood consequently stagnates, and after a time coagulates behind them. Such clots occur in the course of many exhausting diseases, as phthisis, cancer, in which thrombosis is materially facilitated by the quiescent state of the patient. Careful examination of the sites of recent thrombi is said to have demonstrated

absence of endothelium, but this is hardly proof that alteration of the endothelium was the cause of the thrombosis, for the cells may well have disappeared secondarily.

Sometimes abnormality of surface is insufficient to cause extensive clotting until retardation of the blood-stream is added. In the aorta we sometimes find calcareous plates bare, but with little or no adherent fibrin. In aneurisms the wall is always abnormal and the circulation is already retarded; but sufficient clotting to effect a cure may not occur until by treatment we still further slow the current and prolong the contact of the blood with the abnormal surface. In varicose veins, which are frequently the seats of thrombosis, the endothelium, owing to imperfect nutrition, can scarcely ever be healthy, though it may not be so defective as to excite coagulation.

4. **Certain conditions of the blood** favor coagulation and promote the occurrence of thrombosis. It is said that the tendency to coagulate is increased in the later months of pregnancy and after profuse hemorrhage. To whatever cause it may be due, an increased tendency of the blood to coagulate is probably never more than a predisposing cause of thrombosis. In septic fevers thrombosis is not uncommon at points having no direct relation to a wound. This has been attributed to the breaking up of leucocytes in large numbers, which is said by Schmidt and his pupils to occur: it has been shown that injection of leucocytes in large numbers into the circulation of animals is followed by their rapid disintegration and local or even general thrombosis. We presume that Wooldridge would explain this by the setting free of lecithin. In all these cases a failing heart and flagging circulation, the causes of ordinary marasmic clotting, are present. Perhaps desquamation of endothelium (p. 216) occurs; and it is possible that organisms also may play a part in the process. This seems particularly likely in those frequent cases of venous thrombosis, often going on to puriform softening and secondary phlebitis, which occur side by side with erysipelas, pyæmia, etc., and which have gained for "phlebitis" a place amongst hospital diseases.

CHARACTERS OF, AND DIFFERENCES BETWEEN, CLOTS AND THROMBI.—The ordinary red clot of blood drawn from a vein, the "buffy" clot of inflammation or of delayed coagulation, and the white clot free from red corpuscles obtained by whipping blood with anything having a large rough surface, show the

characters and modes of formation of the thrombi with which we have to deal.

Post-mortem coagula in the heart are generally buffy, the thickness of the uppermost pale layer varying directly with the time which elapses before the heart-substance becomes so altered as to allow coagulation to begin. Both in the heart and vessels coagulation occurs in that part of the blood which is farthest removed from the influence of the wall; hence the smaller the vessel the later does post-mortem clotting occur. Such clots are red, soft, watery, never adherent, do not completely fill the vessels, and can be easily drawn out of them as long strings.

Clots formed in the heart just before death connect post-mortem clots and thrombi. These are probably partly due to "whipping" by the chordæ tendineæ, etc. of the blood, which tends to stagnate when the heart is too weak to empty its cavities. As would be expected, they are more or less uniformly decolorized, and, though not adherent, are often so much entangled among the chordæ, etc. that they cannot readily be removed. From their longer duration and more complete contraction they are firmer and less watery than post-mortem clots.

Thrombi or ante-mortem clots are of two kinds, **red** and **white**, according as they originate from *quiescent* or *circulating* blood. In the former case, as seen in an artery or vein after ligature, more or less of the stagnant blood on either side of the knot coagulates into an ordinary **red** clot—soft, uniform on section, and adherent to the vessel-wall where this is injured. The thrombus then contracts, still adhering to the wall, becomes drier and less elastic, but is still red. This is the state in which a red thrombus is generally found.

But when coagulation occurs in blood *which is still circulating*, as in the sac of an aneurism or on a cardiac vegetation, a **white** or **mixed** thrombus results. According to Zahn, who studied the formation of such clots under the microscope in small veins irritated by a small crystal of salt placed near, the abnormal surface causes each successive quantity of blood which passes to leave upon it a little fibrin and some of its most sticky elements—leucocytes; whilst if the blood-stream is languid more or fewer red corpuscles remain in the thrombus, rendering it mixed. But later observers have shown that innumerable blood-plates (microcytes), and not leucocytes, are deposited upon a thread passed through a vessel, and also upon the adventitia of a severed artery within which the cut vessel has retracted. Moreover,

an examination of old clots in aneurisms has convinced Osler that they, too, consist of microcytes, and he consequently regards leucocytes as of little importance in the formation of thrombi. These thrombi are **grayish-white** or **reddish**, firmly adherent to the wall; and it is peculiar to them that they are often **stratified**. This is probably due to variations in the rate of deposition of the fibrin, in the blood-pressure to which it is subjected, and such-like physical conditions. Frequently white and reddish layers alternate.

A thrombus may be "parietal" or "obstructive," causing partial or complete occlusion of the vessel. Once formed, it tends to extend by deposition of more fibrin on its surface. As a rule, this extension is checked by the rapidity of flow at the level of the first large collateral branch in each direction; but sometimes, especially in veins, thrombosis becomes "continued," and one clot may extend from the foot to the cava. Both in arteries and veins extension is always chiefly toward the heart, though it may occur also in an opposite direction. These thrombi generally adhere to the wall throughout, but sometimes they do so only at their points of origin.

In the capillaries coagulation occurs only as a result of necrosis or grave injury of the capillary walls; for they are so small that, so long as they are living, their influence in preventing clotting will act upon the whole of the contained blood (Lister), and consequently thrombosis does not extend into them so long as there is sufficient blood-supply to keep them alive.

LATER CHANGES IN THROMBI.—These are—decolorization (when red), resolution, organization, calcification, softening (simple and infective), and putrefaction.

Decolorization.—The first change in a red thrombus is a breaking-down of the red corpuscles; their stromata become unrecognizable, the hæmoglobin is set free and in great part absorbed, but some may remain as granular hæmatoidin. As a result, the thrombus loses its deep-red color. The process begins in the centre, and takes weeks or months before it is at all complete.

Resolution.—That many thrombi disappear is certain from such facts as that repeated bleedings were effected at long intervals from the same vein when it was the custom for people to be bled every "spring and fall," and from the re-establishment of the circulation through superficial veins in the leg or spermatic veins which are known to have been thrombosed. The steps of the process are not

known. In cases of death from septic poisoning appearances found in vessels which have been tied occasionally indicate that thrombi formed before the onset of the fatal disease have broken down.

Organization has been studied mainly in thrombi forming as the result of ligature. The effect of the application of a ligature is usually to cut through the middle and internal coats of the vessel; these contract and retract somewhat, turning up and down into the lumen of the vessel; and the constricted external coat is all that is left in the grasp of the noose. In a few hours a red thrombus forms, conical in shape, and adherent by its base to the inverted inner and middle coats. It extends for two or three days, and finally reaches the level of the first collateral branch—often, for some unknown reason, stopping short of this on the distal side. Meanwhile, it has become firmer, drier, and more widely adherent about its base to the artery. This adhesion progresses as the thrombosed piece of vessel contracts upon the clot, until it becomes universal. By the second day a buffy nodule may be seen in the base of the deep-red thrombus, and it rapidly increases, so that in a week or two the color of the clot has disappeared. After some weeks or months this decolorized plug is found

FIG. 73.

Section of an Arterial Thrombus Thirty-seven Days old: *a*. New blood-vessels. *b*. Leucocytes and anastomosing cells. (Rindfleisch.)

to have been replaced by connective tissue intimately united with the artery, which has the appearance of a firm fibrous cord. The microscope gives the following explanation of the process: The red thrombus consists of red corpuscles, with a few white, in the meshes of a fibrin-coagulum. The buffy nodule which grows into the base of the clot is formed of small round cells, which at first are undoubtedly leucocytes migrated from the vasa vasorum injured by the ligature.

But there is a difference of opinion as to the origin of those formed after (say) the third day. By this time the cells of the part have recovered from the injury done them by the wound and ligature; and it is stated by some (Riedel, Cornil, and Ranvier) that the endothelial cells multiply and send rod-like processes into the clot, and that these are henceforward the source of the invading cells. Others deny this, and maintain that the new cells are all leucocytes. Senftleben secured between double ligatures pieces of vessels and put them into the abdomens of rabbits—an experiment which is practically repeated in the bits of vessels which lie *beyond* the ligature in all aseptic stumps. He found that they became filled with connective tissue containing well-developed spindle-cells, and concluded, therefore, that the development of the thrombi during life also depends upon migrated white corpuscles, and not upon the endothelium. Obviously, however, proof of the ability of white corpuscles to form connective tissue does not exclude endothelium from doing so likewise as a regenerative process. However formed, the cell-mass is penetrated by blood-vessels, which form as in granulation-tissue (p. 260). The cells become spindle-shaped or branched (Fig. 74), fibrillation appears either in them or in the ground substance between them; many cells disappear as the fibres increase, the latter contract, and many vessels are obliterated, the result being the fibrous cord above mentioned. This is called organization of a thrombus; but it is evident that the original thrombus disappears entirely, and has nothing to do with the process which goes on in the round-celled mass, of the origin of which we are uncertain. The vessel-wall is converted into fibrous tissue and blends with that of the clot.

FIG. 74.

Longitudinal Section of the Ligatured End of the Crural Artery of a Dog, Fifty Days after the Application of the Ligature, showing the newly-formed vessels in the thrombus and their communication with the vasa vasorum. *Th.* Thrombus. *M.* Muscular coat. *Z.* External coat and vasa vasorum. × 20. (O. Weber.)

In certain cases channels are formed in the connective tissue which communicate both above and below with the lumen of the

vessel, and thus the circulation is more or less completely re-established. They are probably due to dilatation of the vessels of the thrombus (though why this should occur in some cases and not in others is unknown), and give rise to the *sinus-like degeneration* of Rokitansky. It is especially common at the junction of the common iliac veins in cases of "white leg," leading to more or less perfect recovery. It is rare in arteries.

Organization is most frequent in uniform, unstratified thrombi, and especially in those occurring in arteries. But long clots of this kind, such as occur after ligature of the carotid low down, and large laminated thrombi, like those in aneurisms, may long remain as more or less granular masses of non-irritant fibrin without any sign of organization.

Calcification.—This occurs in some clots, giving rise to phleboliths. They are especially common in the prostatic plexus.

Softening.—1. Simple. A thrombus which undergoes neither of the previously described changes often softens. This, in the majority of cases, is due simply to the chemical changes which the constituents of a clot undergo when dead but aseptic, and results in the formation of a more or less fluid, pappy substance, which has a red or white color according as it originates from a red or white thrombus. To the naked eye in the latter case it looks much like pus, and the change used to be spoken of as suppuration or **puriform softening** of a clot. But Virchow pointed out that the fluid consisted of the débris of corpuscles and fibrin—albuminous, fatty, and pigmentary granules. There may be a few recognizable white corpuscles in it which have probably migrated from without. The outer laminæ generally form a firm case for the softened central part, and if the softening approach the surface, fresh protective clot often forms at the point; but the encasing clot may be perforated and the contents discharged into the circulation. The larger particles will give rise to embolisms, probably too minute to cause symptoms, and circulation is re-established through the thrombus, the process constituting what is known as **canalization** of a thrombus.

2. **Infective.**—But in certain cases of **puriform** softening, to the naked eye similar to the above, all the symptoms of septic poisoning occur: acute suppurative inflammation of the vein-wall is shown by the microscope, and any portions of the clot which enter the circulation are so intensely irritating as to cause suppuration where they lodge. (See "Pyæmia and Septicæmia.") The difference between

the two cases is this: in the latter form of softening micrococci are constantly present, and it is to them that the infective properties of the broken-down clot are due. In the great majority of these cases the veins affected lead directly from a wound, and then the mode of entry of the specific micrococci is evident. In a small number of patients, also with wounds, the thrombosis and softening occur in veins having no kind of direct connection with the wound; here, too, the organisms enter by the wound, and in some cases at least the thrombosis is secondary to a general septic infection. Finally, there remain a few instances in which no pathological breach of surface could be found for the admission of the germs: it is thought that in these they must have passed into the blood through the alimentary or respiratory mucous membranes.

Putrefaction.—This rare change is due to the entry into the clot from some very foul, and often gangrenous, surface of the bacterium termo and other germs, the growth of which converts the thrombus into a stinking yellow-red fluid which is highly irritating.

RESULTS.—The results of thrombosis comprise certain changes in the walls of the vessels, more or less obstruction to the circulation, and embolism. These must be considered separately.

1. Changes in the Vessels.—More or less alteration in the wall of the vessel is an invariable consequence of the formation of a thrombus. When the thrombus undergoes a process of organization it becomes, as already described, intimately united with the vascular wall. The latter in the first place becomes infiltrated with cells and considerably thickened, but ultimately, together with the thrombus, gradually atrophies. It is when the thrombus undergoes a process of infective puriform softening that the most important changes of an acute inflammatory nature take place in the vessel. They are due to the irritation of the decomposing thrombus, and are most frequently observed in the veins, where infective thrombi are most liable to occur. The walls of a vein within which a thrombus is undergoing puriform softening are considerably thickened, so that to the naked eye it resembles an artery. The inner surface has lost its translucency and is of a dead, opaque color. The adventitia and middle coats are injected and present numerous hemorrhagic points, which are often visible through the intima. The swelling of the wall is due to dense infiltration with leucocytes, which conceals all normal structure, and the innermost cells die and are shed into the

lumen of the vessel. Small collections of pus may be seen in the external and middle coats. The neighboring tissue may also become involved. These acute inflammatory changes in veins constitute what is known as **suppurative phlebitis.** Although most frequently due to thrombosis, they may occur also as the result of extension from adjacent suppurating tissues, in which case the thrombus, which also undergoes puriform softening, is *secondary* to the phlebitis. (See "Inflammation of Veins.") Similar changes are observed in the arteries. Septic arteritis, extending to a ligatured artery from a putrid wound, was formerly most important, being the common cause of secondary hemorrhage now rarely seen.

2. **Obstruction to the Circulation.**—The consequences of the obstruction to the circulation which results from the formation of a thrombus will depend upon the rapidity and cause of its formation, the nature and size of the vessel obstructed, the situation and number of the collateral branches, and the force of the circulating current. The rapidity with which the obstruction is effected is of considerable importance, inasmuch as the more gradual this is, the longer is the time allowed for the establishment of a collateral circulation. For this reason the interference with the circulation caused by thrombosis is, for the most part, less marked than that which results from the more sudden obstruction caused by embolism. The cause of the thrombosis is important for the reason already stated—viz. that in that which results from retardation of the circulation the coagulation does not extend into the capillary vessels unless necrosis occurs.

In the veins, when thrombosis occurs in a vessel of small size and when collateral branches are numerous, as in the prostatic or uterine plexuses, the circulation is but little interfered with and no symptoms of obstruction result. If, however, the main trunk of a large vein, as the ilio-femoral, becomes obliterated, the obstruction is followed by mechanical hyperæmia, the extent and duration of which will depend upon the facility with which the circulation can be restored by the collateral vessels. It must be remembered, however, that the valves in veins, when they exist, may, by preventing back-flow, offer a great impediment to collateral circulation. Thrombosis in the above-named vein frequently occurs, as already stated, in the latter stages of many chronic debilitating diseases, especially in phthisis; also in the puerperal state, where it gives rise to the condition known as **phlegmasia dolens.** As the femoral is almost the only vein which carries blood

back from the lower limb, the effect of sudden blocking of it is marked. At first perhaps cyanotic, the limb becomes swollen, pallid, white, painful, and too tense to pit, and there is often more or less tenderness along the vein, which feels enlarged, hard, and knotty. These symptoms vary greatly in amount, and to them are sometimes added those of lymphangitis and cellulitis. The extent of the thrombus—*i. e.* the number of collateral branches which it blocks and the strength of the circulation—will do much to account for the amount of œdema; and it is probable that the more acute inflammatory symptoms are of septic origin. The circulation is usually ultimately restored; but if the impediment has been of long duration, the tissues become thickened, and the limb is left in a hard, indurated, and somewhat enlarged condition.

The results of obstruction in arteries have been already considered in the chapter on Local Anæmia (p. 203). It is in tissues with "terminal" arteries that the interference is most marked, and here hemorrhagic infarction, which so often results from embolism, may occur, although, owing to the more gradual obstruction of the circulation, it is less likely to do so. (See "Embolism.")

3. **Embolism.**—Portions of the thrombus may be carried away by the circulation, thus constituting embolism. This, which is the most important result of thrombosis, will be considered in the following chapter.

CHAPTER XXVII.

EMBOLISM.

EMBOLISM is the impaction of solid substances circulating in the blood in vessels which are too small to allow them to pass. The solid substances are termed **emboli**, and are very various in their nature.

By far the most frequent sources of emboli are thrombi, portions of which are carried from the seat of their formation by the circulation. Emboli may, however, originate independently of thrombi: vegetations and calcareous or atheromatous masses separated from the valves of the heart or from the inner surface of arteries; portions of new growths, as carcinoma, which, having perforated the vessels, have been carried away by the current; parasites which have made their

way into the interior of vessels; fluid fat which has escaped from the fat-cells and entered open lymphatics, as occasionally occurs in fractures and contusions; pigment-granules and other substances,—may all constitute emboli.

A thrombus may give rise to emboli in two ways: A piece may be swept off from a firm, undegenerate clot; or the thrombus may soften, and the results of this process be discharged into the circulation, when any particles too large to pass through the finest capillaries will give rise to embolism. Portions of a parietal thrombus not filling the vessel may readily be carried away by the passing current. Perhaps, however, the most frequent way in which a thrombus gives rise to embolism is by the breaking off of its conical cardiac end, which often projects a little way into the cavity or over the mouth of a vessel in which the current is too strong to allow of its further progress (Fig. 75). Some sudden movement or exertion often determines in these

FIG. 75.

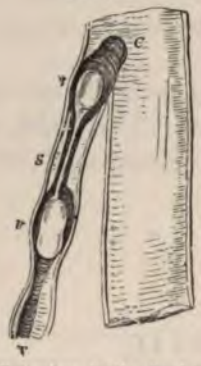


FIG. 76.

FIG. 75.—A Thrombus in the Saphenous Vein, showing the projection of the conical end of the thrombus into the femoral vessel. *S.* Saphenous vein. *T.* Thrombus. *C.* Conical end projecting into femoral vein. At *v v*, opposite the valves, the thrombus is softened. (Virchow.)

FIG. 76.—Embolus impacted at the Bifurcation of a Branch of the Pulmonary Artery, showing the formation of thrombi behind and in front of it, and the extension of these as far as the entrance of the next collateral vessels. *E.* Embolus. *t t.* Secondary thrombi. (Virchow.)

cases the separation of the embolus. It is especially venous thrombi which give rise to embolism, the veins of the lower extremity and jugular veins being amongst the most common sources. Emboli from cardiac thrombi are also exceedingly common, whilst those from arterial are the least frequent.

Emboli become arrested in the first vessels they meet with which

are too small to allow them to pass. And, naturally, the seat of impaction will usually be at the bifurcation of the vessel or where, from the giving off of large branches, the calibre diminishes suddenly (Fig. 76). The particles may be so small as to pass through even the finest capillaries, when they give rise to no symptoms; or they may pass through large capillaries to be arrested in a finer set beyond; but as a rule they become impacted either in the first set of capillaries which they come to, or in some larger vessel between this set and their seat of origin. Thus, emboli originating in the systemic veins or in the right cardiac cavities will most commonly become arrested in the vessels of the lungs; those originating in the arteries, the left cardiac cavities, or the pulmonary veins, in the systemic arteries and capillaries, especially in those of the spleen, kidneys, and brain; and those originating in the portal venous system, in the hepatic branches of the portal vein. With the exception, therefore, of emboli originating in the portal system the seat of arrest is the arteries or capillaries.

Emboli are carried usually in the direction of the main current; hence those carried by the aortic stream pass into the thoracic aorta more commonly than into the carotid and subclavian vessels, and into the left carotid and renal artery than into the corresponding arteries of the opposite side. Gravitation also influences the direction in which they are carried, especially those of large size, which move somewhat more slowly than the blood-stream; hence they are more common in the lower lobes and posterior parts of the lungs than in the superior and anterior portions of these organs.

It is not uncommon to find that the finer vessels of an area of which the supplying artery is plugged also contain emboli. This may be accounted for in two ways: If, as is frequently the case, the arrest takes place at a point of bifurcation, the embolus may partially fill both branches, allowing a small stream of blood to pass; this may break off portions of it, and so cause secondary emboli, which become impacted in the smaller divisions of the above main trunks. The second mode is by the detachment of several small emboli from some distant source, which subsequently yields a mass large enough to stick in the main trunk; for it is found experimentally that small bodies injected at intervals into the jugular vein are sometimes swept into the same division of the pulmonary artery.

The amount of obstruction which immediately follows the arrest will depend partly upon the nature of the embolus itself, as well as upon its size and shape. If the embolus be from a soft, recently-

formed thrombus, it will adapt itself to the cavity of the vessel, and so completely and quickly occlude it. If, on the other hand, it is irregular in shape and firm in consistence, as when derived from a calcified cardiac vegetation, it may not fill the vessel, but allow a small current of blood to pass it.

The arrest of the embolus, and the consequent obstruction to the circulation, is followed by the formation of **secondary thrombi** behind and in front of it, which extend as far as the entrance of the first large collateral vessels (Fig. 76). If the embolus does not completely fill the vessel, coagulum is deposited in successive layers upon its surface until the occlusion of the vessel is complete, and then the secondary thrombus extends, as in the former case, until it meets with a current of blood strong enough to arrest its progress. If the embolus is a portion of a soft thrombus, it will in most cases be impossible to distinguish it from the secondary thrombus which surrounds it. If, however, it is a calcareous mass or a portion of an old thrombus, it may usually be distinguished from the more recent secondary coagulum.

Emboli may in rare cases become absorbed. They may also, when derived from thrombi, become organized or soften. The changes in the secondary thrombi are similar to those already described as occurring in the primary (p. 219).

RESULTS.—The results of embolism are—(1) those depending upon the simple obstruction to the circulation, and (2) those produced by the irritation of the emboli themselves.

1. OBSTRUCTION TO THE CIRCULATION AND ITS RESULTS.—We have already seen that obstruction from embolism can occur only in arteries, capillaries, or the portal vein, which differs from an artery chiefly in its lower blood-pressure; and as obstruction to capillaries, unless it be very extensive, makes little difference to the circulation in a part, we have to consider mainly the results of arterial occlusion. The more sudden and complete this is, the more marked are the phenomena due to it.

Even sudden complete obstruction of many arteries (as a second or third branch of the mesenteric or the radial) is practically without effect upon the circulation, which is carried on through the large vessels with which they anastomose. Easy as it would seem for the circulation to be carried on after obstruction of a vessel going to the

circle of Willis, occasional deaths from cerebral softening after ligature of the common carotid seem to show that it is not so easy as it appears.

In other cases there is more or less difficulty, perhaps amounting to impossibility, in effecting the re-establishment of the circulation. This is owing to either the small number and size of the vessels anastomosing with branches of the obstructed trunk beyond the obstruction, or to disease of these vessels preventing the dilatation of which, in health, they would be capable. We often see this after ligature of the femoral: the limb becomes pale and its temperature falls many degrees; usually it remains so for several hours; then, when all goes well, it gradually becomes some degrees warmer than its fellow, the superficial vessels especially being fully dilated and the circulation rapid through them; this dies away slowly, and the part may ultimately remain abnormally cool. Between complete recovery and death of the part below the obstruction all stages are met with—from death of a toe upward. The part which ultimately dies may remain pale and bloodless and mummify; but usually it becomes more or less swollen with blood driven into it under pressure insufficient to send it back through the veins; fluid and cells pass into the tissues, and moist gangrene results. Similarly, embolism of an ultimate branch of the mesenteric, with secondary thrombosis obstructing the vessels on either side, will lead to an infarcted state of a small segment of bowel with hemorrhage into its lumen, probably ending in recovery; but embolism of the main trunk of this vessel causes gangrene of the whole intestine.

Lastly, there is the "terminal" artery, which has no arterial anastomoses: when this is obstructed re-establishment of the circulation in the area it supplies is impossible, for the pressure in the surrounding arterioles is insufficient to drive the blood through the second set of capillaries (those of the obstructed artery) and on through the vein. From the mode of distribution of the vessels the area deprived of blood has more or less the shape of a rounded cone with its base resting on the surface of the organ: in section from base to apex it of course appears triangular (Figs. 77 and 78). It is surrounded by a zone of arterial redness in recent cases, due to full dilatation of the surrounding capillaries, but the area itself may remain of pale-yellow color, all naked-eye structure being lost, or it may assume a black-red color, like damson cheese, from infiltration with red blood-corpuscles, and so swollen that its base forms a slightly rounded projection on the sur-

face. These characteristic lesions are called respectively **white** and **red infarcts.**

With regard to the mode of production of red infarcts two very different explanations have been offered by Cohnheim and Litten respectively.

According to Cohnheim, the first effect of the plugging of a terminal artery is the stoppage of all supply through it; the arterioles empty themselves by contracting, and pressure in them is reduced to *nil;* venous pressure, though low, is in excess of this, and blood regurgitates from the veins to fill the capillaries and arterioles beyond the stoppage; as may be seen with the microscope in a frog's tongue of which one lingual artery has been tied. The arteries round about the area dilate, and their capillaries become full of blood; but even now the force of the stream in the latter is sufficient to overcome the resistance in only a few of the outlying capillaries of the obstructed area. Consequently we should find such an area dark from containing stagnant venous blood, but surrounded by a ring of arterial redness; and soon the darkness is increased by the escape of red corpuscles into the tissues, without any rupture of vessels, just as happens in venous congestion (p. 209). Finally, secondary thrombosis of the vein and vessels in the area is said to occur (Fig. 77).

FIG. 77.

Diagram of a Hæmorrhagic Infarct: *a*. Artery obliterated by an embolus (*e*). *v*. Vein filled with a secondary thrombus (*th*). 1. Centre of infarct which is becoming disintegrated. 2. Area of extravasation. 3. Area of collateral hyperæmia. (O. Weber.)

The changes which result from deprivation of arterial blood were studied experimentally by Cohnheim. If the ear of a rabbit be emptied of blood, ligatured at its root for from eight to ten hours, and the blood be then allowed to circulate, the organ becomes exceedingly vascular, red, swollen, and œdematous, and when examined microscopically the vessels are found to be dilated, and numerous white blood-corpuscles to have escaped from them into the surrounding tissue. The more prolonged the anæmia, the more abundant is the infiltration with leucocytes; and when the obstruction has lasted twenty-four hours, small extravasations of red corpuscles also occur. If the ligature remain on for forty-eight hours the ear dies. Cohnheim concluded that when blood-vessels with their vasa

vasorum are deprived of circulating blood for a sufficient length of time, they lose their power of retaining the blood, and allow, first the liquor sanguinis and leucocytes, then red corpuscles, to escape from them, the escape taking place only through the capillaries and veins. The whole process can be watched in the tongue of a frog to the base of which a ligature has been applied. For the walls of blood-vessels to be thus altered, interference with the circulation must be very complete—a very little vascular supply serves to prevent the above phenomena; but imperfect nutrition is a step toward death, and must render tissues less resistant to injury—a wide-reaching fact, which must always be borne in mind. These observations explain all changes from œdema to moist gangrene, above given, which may follow ligature of the main artery of a limb, especially the femoral.

Cohnheim thought that when emboli blocked terminal arteries, the result was almost always hemorrhagic infarction; and that exceptions to this rule were due either to the veins of the part being valved or thrombosed so that regurgitation was prevented, or to the part being so placed that gravity favored strongly the return of blood by the veins; in which case the area remained pale and bloodless. Some apparent exceptions were owing to the existence of fine arterial anastomoses with certain of a set of arteries, the great majority of which are really terminal; thus anastomoses of the bronchial artery with the pulmonary might sometimes ward off infarction in the lung. One reason why infarcts are so much commoner on the surface than in the substance of an organ is (he said) that in the former situation the whole base is almost absolutely cut off from collateral supply.

Litten[1] disputes the truth of Cohnheim's explanation of the whole process of infarction. He shows that the infarction of the kidney which follows ligature of the renal artery is not due to regurgitation from the renal vein, for it is even more intense when the renal vein also is tied. The kidney then swells greatly, becoming first congested, then infarcted. The congestion begins in the subcapsular zone of the cortex and at the bases of the pyramids where the pelvis is attached, and it is due to the continued supply of the organ by small arteries (now much dilated) which spring from the lumbar, suprarenal, and phrenic (Ludwig), and pierce the capsule, and to others from the spermatic which run up along the ureter. If the renal vein is left

[1] "Unters. ü. d. hämorrhag. Infarct, etc." (*Deutsche Zeitschr. für klin. Med.*, Band I. Heft 1).

open, the kidney swells more slowly, because some of the blood entering from these arteries escapes by the vein; the stream is therefore away from, not toward, the kidney. But the most perfect proof that the infarction is due to supply through these arteries, and not to venous reflux, is afforded by this experiment: the renal artery is rendered truly "terminal" by shelling the kidney out of its bed of fat, and the artery is then tied. Regurgitation should now occur from the open vein, but, as a rule, it fails to do so. A slight congestion of the organ sometimes occurs, but the gland remains much lighter and smaller than its fellow, of which the renal artery only has been tied, and never becomes the seat of hemorrhage *per diapedesin*. It would seem, therefore, that in many cases the pressure in the renal vein is not sufficient to overcome the resistance of the capillaries and to produce an injection of them with blood when the main artery and its small collaterals are tied; much less would it do so when the latter are pumping blood in beneath the elastic capsule, and thus increasing the intracapsular pressure. If by coughing, vomiting, etc. the pressure in the renal vein is raised, infarction is more likely to occur; and it is produced in its severest form by clamping the vena cava inferior above the entry of the renal vein. These observations were extended with similar results to the spleen and lung.

When a truly "terminal" artery is blocked, no infarction occurs in the great majority of cases; its area remains pale and anæmic, and microscopic examination reveals no trace of red corpuscles. This is seen in cases of embolism of the cerebral arteries (white softening) and of the central artery of the retina.

When an artery becomes blocked in a part (*e. g.* limb) of which the veins are valved, no reflux can occur, but infarction may. It is rare, because such parts have a rich arterial supply, but it may follow blocking of the main artery. (See above.)

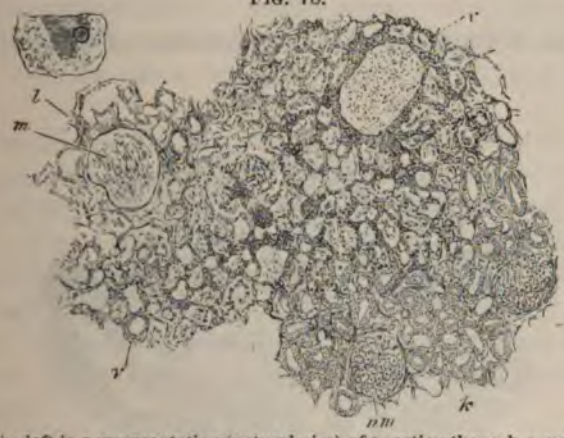
Litten agrees with Cohnheim that the red corpuscles escape by diapedesis, but simply on account of the stretching of the capillaries and small veins by the mechanical congestion. It begins almost at once after the application of the ligature, before anæmia has had time to effect any marked change in the vessel-walls; and no escape occurs in a kidney shelled from its capsule if a ligature on the renal artery be cut after three or four hours.

It would seem that the true reason why red infarcts are found so frequently on the surfaces of the organs in which they occur is, not that the base is almost entirely cut off from blood-supply, but that

here we have entering small capsular arteries through which blood is still driven into the area.

Litten's experiments seem to be conclusive in favor of his view. Cohnheim's regurgitation theory probably holds good for a few cases,

FIG. 78.



Above on the left is a representation (natural size) of a section through a recent infarct of the kidney: the circle marks roughly the part magnified and drawn in the main figure. *k* points to healthy kidney; *nm* to a normal Malpighian tuft; *v* to an area in which the vessels are crammed with red corpuscles, and the tissues are more or less degenerate; *l* and *m* to kidney substance and a Malpighian tuft which are too degenerate to stain.

and we must remember in its favor that in the majority of cases in which simple embolisms from cardiac valves occur there is "back-telling" (p. 36) upon the lungs and venous pressure is abnormally high. With regard to Cohnheim's experiment on the tongue of the frog (p. 254), from which he drew a general conclusion, the resistance offered to regurgitation from the veins by the capillaries of the lax tongue is probably much less than that offered in the firm kidney within its elastic capsule.

Red infarcts occur chiefly in the lungs, spleen, kidney, and sometimes the intestine.

A **white infarct** may be primary, especially in the brain or retina, but also in other organs; or secondary, being due to decolorization of a red infarct. Examination enables us to see more clearly than in the red **the effect upon the tissues** of cutting off the blood-supply: shortly they undergo necrobiosis (p. 41). The essential cells of the part, deprived of blood, speedily become swollen and structureless (undergoing **coagulation necrosis**), and then undergo fatty degeneration, thus giving rise to the white wedge. This change is well

seen in Fig. 78, and also in Fig. 79, in which the dead tissue is shown separated from the living by the hyperæmic zone. When the white infarct is a late stage of the red it will contain granules and crystals of blood-pigment. With regard to the relative frequency of primary white and red infarcts in organs where both occur, there is still much doubt.

Cessation of function soon follows cessation of nutrition, and the

FIG. 79.

Embolic Kidney: From a case of aneurism of the abdominal aorta; many small yellow-white patches were scattered through the cortices of the organs. Essential cells fattily metamorphosed, connective-tissue cells still capable of staining. × 200.

effects of this may be extremely serious; thus, plugging of one of the larger cerebral arteries is generally followed at once by sudden loss of consciousness and paralysis (apoplexy); embolism of the pulmonary artery, by sudden asphyxia; or of the coronary arteries, by sudden paralysis of the heart.

Sometimes sufficient nourishment is maintained by transudation from surrounding parts to keep the connective-tissue stroma alive; its nuclei then stain in sections (Fig. 79). A very important point is that all vessels do not resist equally the effects of anæmia, those of skin and muscle being most resistant; those of brain and intestine least. Strangulated gut is like a tied-off ear, but it dies much sooner. This power of resistance varies in individuals.

2. **IRRITANT EFFECTS OF AN EMBOLUS.** — A **simple embolus,** such as a bit of non-infected fibrin or a fragment of a calcareous plate, causes slight irritation of the vessel where it lodges. Such an embolus, with its secondary thrombi, will usually be absorbed or become organized. Rarely, such inflammatory softening of the

vessel-walls results from this irritation that it yields before the blood-pressure, and an aneurism results. This is now held to be the pathology of most aneurisms occurring in people too young to be suffering from atheroma or acquired syphilis; and, as the emboli are usually small or of moderate size, dilatations from embolism affect especially the cerebral arteries and the smaller arteries of the limbs, from the size of the brachial downward. We do not know why, in two apparently similar cases, the artery yields in one and not in the other.

An **infective embolus** is one which has brought with it from its source organisms capable of growing within the body—at all events, in the dead or greatly depressed tissues of an infarct—and which thus infects, or gives rise to bacterial changes at, the spot at which it lodges. The result depends upon the intensity of the irritation which the particular bacteria can excite; in cases of rheumatism they often seem to render the embolus little more irritant than simple fibrin; but in pyæmia the micrococci cause the secondary suppuration. (See "Pyæmia.")

LATER CHANGES IN INFARCTS.—As these depend (1) upon the extent to which the circulation is interfered with, and (2) upon the amount of irritation caused by the embolus, they have been more than hinted at above.

Absorption and Scar-formation.—If the infarct be small and the embolus possess no infective properties, in the case of red infarcts the coagulated blood gradually loses color, becoming brown or yellow, and absorption proceeds slowly. When infarction does not occur, the tissue-changes, which occur equally in the red infarcts, are more clearly seen: lymph reaches the part by transudation from parts around, the cells swell, lose their nuclei, and blend—in fact, undergo coagulation-necrosis (see "Diphtheritic Inflammation"), and thus form the well-known white wedges. The more external portions of the mass of coagulated blood and necrosed tissue become infiltrated with leucocytes, which develop into fibrous tissue; this contracts, and ultimately a depressed scar may be all that remains to indicate the change. For some time, whilst these secondary changes are taking place in the infarct, its most external portions are surrounded by a red zone of hyperæmic tissue. This is exceedingly characteristic.

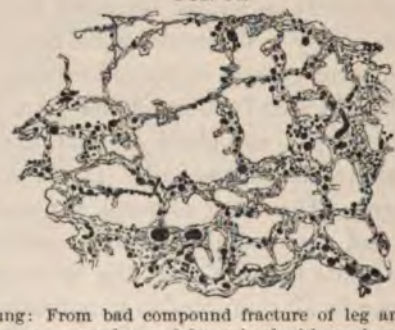
Simple Softening, Absorption, and Scar-formation.—If, however, the infarction is considerable, the central portions may disinte-

grate and soften. This may subsequently dry up and leave a depressed scar.

Infective Softening.—But if an embolus is derived from a part where infective inflammation is going on, it sets up a similar inflammatory process, both in the vessel within which it becomes impacted and also in the surrounding tissues. These septic inflammatory changes lead to the formation of abscesses which are known as **embolic** or **metastatic abscesses.** Microscopic organisms are almost invariably found in these abscesses, and it is to them that the infective properties of the embolus are probably due. No more suitable nidus for their development can well be imagined than a tissue in which infarction and necrosis have occurred, and which is kept moist at the temperature of the body. Infarction, however, is not necessary for the formation of a metastatic abscess. If the metabolism of the tissue in which the embolus lodges does not destroy the organisms, but affords them suitable pabulum, inflammation will ensue. This subject will be considered further in the chapter on "Septicæmia and Pyæmia."

CAPILLARY EMBOLI.—These generally consist of fat, masses of organisms, clumps of white blood-corpuscles, pigment-granules, or air. In fractures, contusions of subcutaneous tissue, ruptures of fatty liver, acute osteo-myelitis, and other morbid conditions in which fat-cells are broken up and the fat set free, the droplets are absorbed by

FIG. 80.



Fat-embolism of Lung: From bad compound fracture of leg and severe subcutaneous laceration. The black masses are drops of fat stained with osmic acid, lying in capillaries and arterioles of alveolar walls. × 40.

the lymphatics and veins, especially when pressure in the part is increased by inflammatory effusion or hemorrhage. Reaching the right heart, they are carried into pulmonary arterioles and capillaries,

where their presence may easily be demonstrated by staining with osmic acid (Fig. 80). One by one these soft and easily-moulded plugs are swept on to the left heart, and distributed by the systemic circulation to other organs, in which also they may be very numerous. For a time fresh emboli are constantly reaching the lungs, but when this ceases the fat-masses are passed on to other organs, and eliminated, in part at least, through the kidneys. This fat-embolism is believed by some to be the cause of death after simple fractures—a very rare event. But as large quantities of fat may exist in the lungs and other organs of animals without causing any symptoms whatever, some scepticism is justifiable. If a sufficiently large number of the capillaries of the lung or any other organ be blocked by fat, its function cannot be discharged; and in the case of several organs this would mean speedy death. It is probable that the lungs always contain, proportionately, many more emboli than any organ supplied by the systemic circulation, and it has been ascertained that half the pulmonary blood-path may be obstructed without disturbing the circulation at large (Cohnheim). We must therefore suppose that, except perhaps in very rare cases, the number of plugged capillaries is kept below some point of danger, at present undetermined, by passage of the fat on to the systemic circulation. In acute osteo-myelitis it is probable that the fat-drops may serve as pyogenic cocci from the seat of inflammation, and cause their impaction in vessels which they would otherwise pass freely through.

Clumps of leucocytes form emboli in septic fevers (Hüter), pigment-granules in ague, and air in entry of air into veins. Here, as in fat-embolism, the air-plugs have little effect: death results only from air injected so quickly and in such quantity that the blood in the right heart is churned into foam, upon which the viscus fruitlessly contracts.

Thrombosis and Embolism of the Brain.

Thrombosis and embolism are the most common cause of **cerebral softenings.**

Softening from Thrombosis.—This is commonly the result of atheromatous, calcareous, or syphilitic changes in the **cerebral arteries.** Such changes cause a diminution in the lumen or a roughening of the internal surface of the vessels, impair their elasticity and contractility, and so favor the occurrence of thrombosis. As a result

of the interference with the supply of blood the cerebral substance undergoes a more or less rapid process of necrosis, such as has been already described (p. 76). The softened portions, when recent and when the obstruction is **rapidly induced,** are often of a reddish color, although with age they gradually become decolorized. In the more gradually induced obstructions the color of the softened tissue is usually white.

Besides thrombosis from arteries we meet also with thrombosis of **cerebral sinuses and veins.** Thrombosis of a sinus may be **primary,** and fall under the heading of marasmic (p. 216), or it may be **secondary** to disease of some adjacent part—*e. g.* of the bone in inflammation of the middle ear; or thrombosis may spread from an inflamed part—*e. g.* orbit—along a vein to the sinus into which it opens. The result is great congestion of all veins opening into the sinus, œdema of the area whence they draw their blood, numerous hemorrhages, especially in the vascular cortex, and more or less softening from impaired nutrition. If thrombosis spreads from a sinus into a vein, the obstruction, and therefore the above phenomena, are most intense.

Softening from Embolism.—The softening resulting from embolism is, for the most part, entirely dependent upon the obstruction to the circulation caused by the embolus and by the resulting thrombosis. It is rapidly induced, and is often attended by the extravasation of blood in its neighborhood, when it constitutes one form of acute red softening. If the interference with the circulation be slight, there may be no extravasation of blood and the process of disintegration may be more gradual, so that the softened portions are white in color, and the condition then more resembles the chronic white softening already described as resulting from degeneration of the cerebral blood-vessels (p. 76). The softened tissue will be white in color also when one of the largest vessels is obstructed, so that a large portion of one hemisphere loses its vitality. The vessel most frequently blocked is the middle cerebral artery in some part of its course, and in the majority of cases it is that of the left side. In almost all cases in which softening of the cerebral substance results from embolism the embolus is arrested in one of the vessels beyond the circle of Willis, because here the circulation cannot be restored by the collateral vessels. It appears, however, that it by no means necessarily follows the blocking of a cortical branch, for commu-

nication between these is much more free than is generally supposed.

Engorgement of the area beyond an obstruction in a cerebral artery does not as a rule occur, but may be so marked as to cause rupture of a large artery beyond the obstruction, and fatal hemorrhage some days after the embolism. From what has been said, this is far more likely in obstruction of cortical than of cerebral vessels. When interference with the circulation is attended by vascular engorgement and extravasation of blood, the softened portion in the early stage is either of a uniform dark-red color or presents numerous red hemorrhagic points. It affects the vascular gray matter of the cortex and great ganglia, rather than the white substance. The softening is most marked in the centre, whilst the hyperæmia and redness may extend some distance around it. Under the microscope the softened portion is seen to consist of broken-down nerve-fibres, altered blood-corpuscles, granules of fat, and the large granular corpuscles already described. (See Fig. 15.) The surrounding capillaries are dilated and filled with coagula, and granular corpuscles envelop their walls. In a more advanced stage all trace of nervous structure is lost, the softened mass becomes decolorized, and passes from a dark-red color to a chocolate, brown, yellow, or even white. It may liquefy and form a cyst with clear contents and a fibrous wall; more commonly, however, it is gradually absorbed, being replaced by fibrous tissue, which contracts; and ultimately a cicatrix, with hæmatoidin crystals, may be all that remains.

Red softening from embolism is often very difficult to distinguish in the post-mortem room from that which results from thrombosis.

CHAPTER XXVIII.

LEUCHÆMIA.

LEUCHÆMIA, or **LEUCOCYTHÆMIA**, is a disease characterized by a considerable and permanent increase in the number of the white corpuscles of the blood, by a diminution in the number of the red corpuscles, and by enlargement of some of the lymphatic organs. The lymphatic organ most frequently involved is the spleen.

This is enlarged in the great majority of cases (splenic leuc
The enlargement of the spleen is sometimes associated with
ment of the lymphatic glands, and sometimes, although mu
frequently, with an increase in the medulla of bones. In ve
cases the lymphatic glands only are involved (lymphatic leuc
and cases have been described by Neumann and others in wh
osseous medulla was principally affected. The lymphoid ti
the intestine may be hypertrophied. In most cases of leucha
overgrowth of lymphatic tissue in other organs occurs sooner
in the course of the disease.

Leucocytosis.—Before proceeding to the consideration
chæmia it will be well to allude briefly to that slight and ten
increase in the number of white blood-corpuscles which h
termed "leucocytosis." This differs essentially from leucha
these respects: that the increase in the number of white corpu
only temporary, is not necessarily associated with any diminu
the number of the red, and is never nearly so great as in leuc
more than forty or fifty being rarely seen in the quarter-inch
the microscope. Such slight and temporary increase in the
of white blood-corpuscles occurs in many conditions. Physiolo
it occurs after a meal and in the later months of pregnancy. I
of the acute pyrexial diseases, especially in those in which
acute swelling of lymphatic structures, as in typhoid and scarl
and in pyæmia, there is often a marked excess of white cor
After large losses of blood also there is an increase, owing to in
pouring of lymph into the blood to make up its mass. Leuc
does not appear to interfere either with the circulation or w
general health.

PATHOLOGY.—The pathology of leuchæmia is still exce
obscure, and will probably remain so until our knowledge of th
iology of the blood and the origin and fate of the blood-corpu
more complete. Physiologically, we know that the white co
originate in the lymphatic organs, from which they pass into th
either directly or through the lymphatic vessels; and it is n
erally believed that the red corpuscles originate from the wh
latter being transformed mainly in the spleen and red
Owing to the enlargement of one or more of the lymphatic
which always exists in leuchæmia, it has been supposed t
increase in the number of the white corpuscles which chara

the disease is due to their excessive production by the enlarged organs, such as occurs in some cases of leucocytosis. Inasmuch, however, as there is not only an increase in the number of white, but a diminution in the number of red, this hypothesis is insufficient to account for the blood-change. Further, lymphatic organs may become enormously enlarged without the production of any leuchæmia. This occurs, for example, notably in the spleen in **splenic anæmia**; which disease, with the exception of the increase in white blood-corpuscles, is precisely similar to leuchæmia; and also in the lymphatic glands in Hodgkin's disease. Although, as already stated, the subject is still involved in much obscurity, the view promulgated by Virchow more than twenty years ago accounts most satisfactorily for the blood-change. It is that the normal transformation of white corpuscles into red is imperfectly performed, so that not only is the number of white increased, but that of the red diminished. It is probable that this diminished transformation of the white corpuscles is the most important element in most cases of leuchæmia, although it may be associated with an increased production. Both the diminished transformation and the increased production take place in the enlarged lymphatic organs; and all we can say at present in explanation of the process is, that the function of one or more of these organs is imperfectly performed. The enlargement of the lymphatic organs is, with little doubt, due to new growth, and not, as has been suggested by some, simply to the accumulation within them of the white corpuscles which exist in such large numbers in the blood.

HISTOLOGY.—Blood.—The diminution in the number of white corpuscles varies very considerably in different cases. A proportion of one white to ten red is quite common, and often there are as many as one to three (Fig. 81). This increase gives to the blood a paler and more opaque appearance than natural. In the earlier stages of the disease the proportion may not be more than one to twenty or forty. The white corpuscles sometimes resemble the natural ones, but often they are somewhat larger and more granular. This is especially the case in splenic leuchæmia, whereas when the lymphatic glands are principally affected many of the corpuscles are usually smaller than natural. Some of them are often more or less fattily degenerated.

The red corpuscles, like the white, vary in the diminution of their number. They may be reduced to one-half or a quarter the normal. They are usually natural in appearance, but sometimes they are dis-

tinctly paler than in health. Occasionally they appear to be unusually soft, and exhibit a tendency to stick together instead of forming the natural rouleaux. In a case of splenic anæmia recently under my care these characters were especially marked (Fig. 82). The diminution in the number and the impairment of the quality of the red corpuscles

FIG. 81.

FIG. 82.

FIG. 81.—Leuchæmic Blood, from a young man aged twenty-four with enormous enlargement of the spleen. × 200.

FIG. 82.—Blood from a Case of Splenic Anæmia, from a middle-aged man with great enlargement of the spleen. × 200.

which exist not only in leuchæmia, but in most cases of great splenic enlargement, account for the anæmia which exists in these conditions. In addition to the red and white corpuscles Klebs and others have found nucleated red corpuscles in leuchæmic blood, and minute, colorless, long, slender octohedral crystals of an albuminous character have been discovered by Charcot and Zenker in the blood, liver, and spleen. The coagulating power of the blood in leuchæmia is much diminished, and when the liquid is allowed to stand the white corpuscles form a creamy layer upon its surface.

Spleen.—In this, which is much the most important organ in the production of leuchæmia, the change is characterized mainly by increased growth. The organ becomes enlarged, and usually enormously so. The enlargement is uniform, so that the shape of the organ is but little altered. The capsule is often thickened, and there are usually adhesions with the adjacent viscera. The consistence in the later stages is commonly distinctly firmer than natural. The cut surface is smooth, of a grayish or brownish-red color, and thickened trabeculæ can often be seen marking it as whitish lines. The Malpighian corpuscles, although they may be slightly enlarged in the earlier stages of the disease, are seldom prominent, and they are often not visible when the splenic enlargement is advanced. In exceptional cases, however, and especially when the lymphatic glands are involved, they may form prominent growths. Sometimes wedge-shaped masses

of a dark-red or reddish-yellow color are seen near the surface of the organ. These are probably infarctions of embolic origin.

When the spleen is examined microscopically its structure is found to be but little altered, the enlargement being due mainly to an increase of the splenic pulp. The trabecular tissue is also increased and thickened, and becomes increasingly so as the splenic enlargement advances. The Malpighian corpuscles are but little increased in size; sometimes they are atrophied.

Lymphatic Glands.—The enlargement of the lymphatic glands is much less in splenic leuchæmia than in those cases in which the glands are primarily and principally affected. In splenic leuchæmia one or more groups of glands are slightly enlarged in about one-third of the cases. The glands are rarely increased in consistence, and are usually freely movable. On section they are of a grayish-red color, often mottled with hemorrhages. Microscopically, the enlarged glands show increase of the pulp and blocking of the lymph-paths.

The **red marrow**, found normally in the bones of the head and trunk of adults and throughout the limbs in the fœtus, is a blood-forming organ. In leuchæmia it may become more highly cellular, and consequently softer and grayer or yellower in color. Further, whereas in the normal growth the red marrow is replaced by yellow progressively from the toes and fingers up to the heads of the femora and humeri, in this disease the opposite change occurs, and the yellow marrow is progressively transformed into red from the trunk toward the extremities of the limbs.

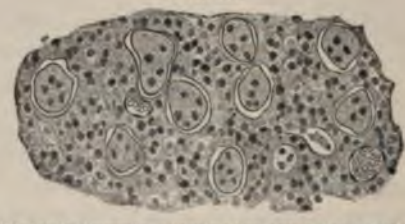
The **follicles of the intestines** may become so much enlarged as to form distinct projections from the mucous membrane, although this is less common than in Hodgkin's disease.

Other Organs.—In the course of the disease a new growth of lymphatic tissue or an infiltration with lymphatic elements usually takes place in non-lymphatic structures, principally in the liver and kidneys, less frequently in the lungs and muscles. The new growth in these organs sometimes forms distinct tumors, but much more commonly exists as an infiltration. How far these lymphoid growths are the result of a hyperplasia of the cells in the interstitial tissue of the organ in which they are situated, and how far an emigration of the leucocytes, which exist in such large numbers in the blood, takes part in their formation, is unknown. The former, however, is probably the most important factor in the process.

The organ which is most frequently affected is the **liver**. Here, in

leuchæmia, the vessels generally are enlarged and distended with whi blood-corpuscles. Accumulations of corpuscles and lymphoid tissu are seen between the acini and extending along the intercellular ne work into the acini themselves, so that the lobules are sometimes see to be clearly mapped out by a grayish-white interlobular infiltratio As this increases the liver-cells become compressed and atrophy, unt ultimately the lobules may be replaced entirely by it. This is we shown in the liver from the case of splenic anæmia, the blood fro which is represented in Fig. 82. (See Fig. 83.) Associated wit

FIG. 83



Liver from a Case of Splenic Anæmia, showing the extensive cellular infiltration involvi the intercellular network. The organ was greatly enlarged, and the new tissue was visible the naked eye between the acini. × 200.

this infiltration there is often a formation of small, round, whitis lymphoid nodules, somewhat resembling gray tubercles. These al are situated in the interlobular tissue. Owing to these changes t liver becomes very considerably increased in size.

In the **kidneys**, which are also frequently affected, the change similar to that in the liver. Here also it consists for the most pa in an infiltration, with which may be associated the formation roundish nodules and masses.

CHAPTER XXIX.

INFLAMMATION.

DEFINITION.—Inflammation may be defined as "the succes of changes which takes place in a living tissue as the result of s kind of injury, provided that this injury be insufficient immedia to destroy its vitality" (Sanderson).

HISTOLOGY.—The exact nature of these changes has been ascertained, for the most part, by the experimental researches of Cohnheim, most of which have been repeated and confirmed by Burdon Sanderson. The method of investigation has consisted in the artificial production of inflammation in transparent parts of the lower animals, and observation of the process thus induced. The parts employed have been the foot, tongue, and mesentery of the frog, the tongue of the toad (the best for many purposes), the mesentery of the rabbit, and the wing of the bat. These have shown that the process is essentially the same in warm- and cold-blooded animals; and by microscopic examination of the lip by reflected light Hüter proved that it is the same in man. The **process of inflammation** comprises—

1st. **Changes in the blood-vessels and circulation.**

2d. **Exudation of fluid and of blood-corpuscles from the vessels**; and

3d. **Changes in the inflamed tissues.**

Though thus separated for purposes of description, it must *not* be supposed that these changes occur in succession in the order in which they are placed; on the contrary, *they all go on together.*

I. **CHANGES IN THE BLOOD-VESSELS AND CIRCULATION.**—Changes in the blood-vessels and circulation are essential to the existence of inflammation, both in vascular and in non-vascular tissues. In the latter, which comprise the cornea and cartilage, they take place in the adjacent vessels from which these tissues derive their nutritive supply. Their nature may be studied in the mesentery of a frog which has been curarized; and they may be thus briefly described:

The first effect of injury of the mesentery—mere exposure to the air being sufficient for the purpose—is to cause **dilatation**[1] of the arteries, which gradully extends to the veins and capillaries. The dilatation of the arteries commences at once, and is not preceded by any contraction. It steadily and slowly increases for about twelve hours, and is accompanied also by an increase in the length of the vessels, so that they become more or less tortuous. It affects the arteries chiefly, then the veins, and the capillaries but slightly. This enlargement of the blood-vessels is associated at the commence-

[1] With certain irritants, as ammonia, a short contraction of the arterioles may be the first result.

ment of the process with an **acceleration** in the flow of blood, which, however, rarely lasts more than an hour, and is followed by a considerable **retardation** in the circulation, the vessels still remaining dilated.

Pulsation is now evident in the smallest arteries and the stream is slow enough to allow of the distinction of individual corpuscles in the capillaries and smaller veins—perhaps even in the arterioles.

It has, however, long been known that the acceleration of the blood-flow in an injured part—the so-called **determination** of blood which was so correctly described more than thirty years ago by Dr. C. J. B. Williams—is not constant, and often subsides without the occurrence of any of the characteristic phenomena of inflammation. Cohnheim consequently states that dilatations of vessels with increased velocity of the blood-current ensuing immediately after the infliction of an injury are accidental. In some cases they are followed by contraction, after which **dilatation with slowed stream** commences. This dilatation with diminished velocity, on the other hand, comes on slowly, is constant, and permanent so long as the cause acts, and must be regarded as the essential vascular change of the inflammation.

Returning to the observation of the frog's mesentery: the retardation of the circulation in the dilated vessels is sometimes seen to take place somewhat suddenly, and is usually first observable in the veins. As the stream gets slower white corpuscles are seen in increasing numbers in the plasmatic layer in the *smaller veins*—rolling slowly along, sticking here and there, and finally coming to a standstill—until these vessels are lined by them as with a spheroidal epithelium (see Fig. 84) often more than one cell in thickness. Some stick also in the capillaries. The time at which this occurs varies greatly; it is the earlier the more severe the injury. This narrowing of the veins by layers of leucocytes, among which there are no red corpuscles, increases the obstruction to the circulation, which becomes slower and slower, both on this account and because the damage is becoming greater. The red corpuscles, with some white, accumulate in the capillaries, which appear as if distended by a red injection-mass. Actual measurement shows that they may be one-fourth larger than natural (Lister, Brücke). After a time all onward movement ceases in the capillaries, and their contents sway to and fro with the pulse. This is the stage of **oscillation**; and it is succeeded by that of **stasis**, in which no movement of any kind occurs, but the blood, though stationary, may remain fluid for as long as three days in the bat's wing (Paget). Finally,

thrombosis or coagulation may take place, but not until the capillary walls are dead. Thrombosis puts an end to that escape of corpuscles from the vessels which will be treated of in the next paragraph.

II. **ESCAPE OF FLUID AND OF BLOOD-CORPUSCLES FROM THE VESSELS.**—The circulatory and vascular changes have been described from beginning to end, as if they were the only phenomena of inflammation. But this is far from being the case. Soon after the veins become lined by white corpuscles the field becomes more and more obscured by the presence of small round cells in the substance of the mesentery. At even an earlier period, though the microscope does not show it, the fluid which naturally escapes from the vessels increases greatly in quantity and changes in quality. So soon as the lymphatics become unable to carry it off, it accumulates in the connective-tissue spaces and causes swelling of the mesentery. These finally become insufficient to hold it, and it escapes on the surface, together with a number of the small round cells. Here a coagulum forms, consisting of fibrin, small round cells, and some red blood-corpuscles. The **false membrane** can be removed and the field cleared for observation until another membrane forms.

a. **Source of the New Cells.**—If a small vein lined by leucocytes be carefully watched, the following changes will be seen, perhaps at once, perhaps not for some time: some of the leucocytes immediately adjacent to the wall gradually sink into it and pass through into the surrounding tissues. Various stages of their passage may be observed. At first, small button-shaped elevations appear on the outer wall of the vessel. These gradually increase until they assume the form of pear-shaped bodies adherent by their small ends to the vessel-wall, and they often send out processes whilst so attached. Cornil and Ranvier say that if an adherent leucocyte is torn from the wall and swept on, the adherent part is "fingered," and v. Recklinghausen has described the part within the vessel (in a tadpole's tail) as sending out processes. Recently Lavdowsky has figured leucocytes passing through vessel-walls in frogs and presenting appearances indicating great activity. Ultimately, the small pedicle of protoplasm gives way and the passage is complete, the corpuscle remaining free outside the vessel. A similar escape takes place, but to a less extent, from the capillaries.

In most inflammations the escape of white corpuscles is far in excess of that of the red; but in the most severe, in which stagnation is induced in a large number of capillaries, the usual state of affairs may be reversed (Fig. 88). From such capillaries red corpuscles

FIG. 84.

Subcutaneous Tissue some distance above Dead Part in a Case of Spreading Gangrene: three veins packed with leucocytes (*l*), which are escaping freely. Round the artery (below) there are none. Many leucocytes outside the vessels have increased in size. × 200.

almost alone pass out, occupy the interstices of the tissues, and give the exudation a hemorrhagic character, whereas if the blood is in motion most red corpuscles pass through the inflamed area whilst the stickier white adhere to the wall. Intensity of injury and vascularity (*i. e.* number of capillaries) determine the proportion of red corpuscles in an exudation. They pass out chiefly from the capillaries, and several often escape in quick succession from one spot, giving rise to a red spot visible to the naked eye as a punctiform hemorrhage. No rupture of vessels occurs, as may be shown by injection.

Both red and white corpuscles at first remain near the vessels whence they have escaped, but they are pushed away by other corpuscles, washed away by the escaping fluid, and the white corpuscles move away by their peculiar power of locomotion. Thus they may ultimately be found far from their source.

But are white blood-corpuscles the only source of those numberless cells of embryonic appearance which crowd the tissues in every

inflammation other than the most trivial? Virchow advanced the view that they all arose by multiplication of connective-tissue corpuscles. Dr. W. Addison in 1842 inferred from his observations that leucocytes passed through the vessel-walls and became pus-cells; and in 1846, Dr. Augustus Waller actually saw them escaping, and described and made drawings of the process. Both concluded that the escaped corpuscles became pus-cells, but their observations were unheeded, and it was not until the process was rediscovered by Cohnheim in 1867 that escape of blood-corpuscles came to occupy an important place in the pathology of inflammation. Cohnheim asserted that all new cells formed in the tissues as a direct result of injury are escaped white corpuscles which have migrated to the spot at which they may be found. And, in spite of the opposition of Stricker and his pupils, proof of the correctness of this view has been given; or perhaps it would be more correct to say that all arguments and experiments in favor of multiplication in inflammation of fixed tissue-cells have been shown to be inconclusive. To prove Cohnheim's view it would obviously be necessary—1, to show that migration of leucocytes will account for all the phenomena observed; and 2, that no multiplication of the fixed cells can occur. Experiments have amply shown that migration of leucocytes will give rise to all the appearances noticed, but it is difficult absolutely to exclude the possibility of multiplication of a fixed cell.

The method adopted to show that leucocytes can produce the appearances attributed to multiplication of fixed elements has been to excise a cornea or other piece of tissue of which the cells were suspected of multiplying, keep it for some days, render it aseptic, and then place it in the peritoneum or subcutaneous tissue of a living animal. Clumps of small round cells were always found in positions normally occupied by tissue-corpuscles: they had been attributed to multiplication of the latter, but this, under the conditions of the experiment, was impossible. The fixed connective-tissue cells lie in spaces and clefts, and the migrating leucocytes, taking the easiest course open to them, invade and accumulate in these spaces and around the fixed cells.

The last stronghold of those who upheld the origin of these cells from multiplying connective-tissue corpuscles was the non-vascular tissues, and especially the cornea. Böttcher showed that after slight central injuries of the cornea with nitrate of silver, which caused no affection of the surrounding vessels, the sites of the corneal corpus-

cles in the neighborhood were occupied by clumps of embryonic cells which he believed could have been formed only by multiplication of the fixed cells. Cohnheim pointed out that the new cells might be leucocytes which had migrated from the conjunctival sac, and Senftleben proved that this was their source. With chloride-of-zinc solution it is possible to kill the corpuscles in a small central area of the cornea without affecting the marginal vessels, and also *without destroying the dense anterior corneal lamina:* under these circumstances the spot remains clear, and no clumps of embryonic cells are found. But if the spot irritated is near the margin of the cornea, the vessels here dilate, and it becomes cloudy from infiltration with leucocytes. And if to central injury not affecting the vessels a cut or stitch through the anterior lamina is added, opacity results from infiltration of corpuscles from the conjunctival sac.

Next, as tending to disprove the possibility of multiplication of fixed connective-tissue corpuscles, we have, first, the *a priori* argument that inflammation is the result of injury—of the action of an irritant, which is more intense than a stimulant—and that the tissues are damaged: it is therefore unlikely that they would begin to multiply; but in using this argument we must remember the atrophic prolification (p. 47) of nuclei which accompanies rapid atrophies. Lister long ago gave the following facts as proofs of depressed vitality in an inflamed part from the earliest stages: The blood tends to behave as it does in contact with dead tissue—*i. e.* to coagulate; the pigment-cells of the frog's skin are paralyzed even by very slight irritation; more severe injury paralyzes muscular fibres, for a dilated arteriole in an inflamed area will not contract when a needle is drawn across it; ciliary action first becomes excited, then speedily ceases—temporarily or permanently—under irritation; the superficial, feebler epidermic cells die and separate after slight injury which the deeper ones survive. All the cells of an inflamed part which were open to investigation were either unable to perform their function or were actually dead. In all inflammations but the mildest Weigert has shown that proper staining will reveal cells which have undergone coagulative necrosis, and the destructive effect of many inflammations is only too obvious. But Lister's views as to the nature of inflammation were at the time rejected, because they would not fit in with the cellular theory of Virchow, which required increased activity on the part of the tissues.

Lastly, prolonged observation (eight or nine days) of connective-

tissue corpuscles of the toad's tongue (Dowdeswell) has shown the absence of all except degenerative changes. It seems almost certain, therefore, that Cohnheim's view is correct—viz. that all new cells found in inflamed tissues as a direct result of the injury which caused the process are escaped blood-corpuscles.

In the less acute forms we find cells which are formed by regenerative processes going on in the cells of the tissues, but these must be sharply distinguished from those of inflammatory origin (p. 110).

β. **Exudation of Fluid.**—As before stated, one of the earliest effects of the vascular changes in inflammation is increased exudation of fluid. Something of this was noted in the microscopic examination of the inflamed mesentery, but other experiments show much more. Lassar tied a canula into a large lymphatic of each hind leg of a dog, stopped the circulation in one leg, and dipped it into water at 54° C., thereby exciting acute inflammation. On removing the fillet the lymph-stream from the canula at once exceeded the normal, and soon reached eight times that on the sound side. At first the fluid was clear, but after a time white corpuscles in increasing numbers made it cloudy, and red corpuscles were found in small numbers. Swelling of the foot began while the flow of lymph was free, evidently because the exudation was too rapid to be conveyed away by the lymph-channels, even when fully dilated. Later in the experiment the flow diminished, partly because exudation diminished as pressure on the vessels (from effusion beneath the skin) rose, and partly from coagulation in and blocking of lymphatics. The lymph collected differed from the exudation-fluid in mechanical hyperæmia in containing a much larger proportion of albumen, more phosphates and carbonates, and in having a much greater tendency to coagulation. This latter property is partly due to the greater number of white corpuscles which it contains. The lymph differed from liquor sanguinis in containing less albumen and having a slighter tendency to coagulate. The composition of inflammatory effusion, however, is not constant. In the most acute inflammations it contains a large number of red corpuscles; in less severe, white corpuscles are in great excess of red. The more severe the process, the more nearly does the fluid approach plasma in its composition and tendencies, whilst in the less severe it becomes very like the fluid in mechanical hyperæmia.

III. **CHANGES IN THE INFLAMED TISSUES.**—The tissues of an inflamed part are softer than natural, watery or solid-

looking, and in either case the component tissues are blurred or altogether indistinguishable. Microscopically, the tissue-elements are at first separated by fluid and obscured by leucocytes and fibrin-filaments; the tissue-cells, when not obscured by leucocytes, are either structureless masses from coagulation-necrosis or are undergoing fatty degeneration: the tissue-fibres are swollen, less distinct, and ultimately degenerate. Red corpuscles are found in greater or smaller numbers in even moderately severe inflammations. The changes in the escaped leucocytes and the actual destruction of tissue will be described under "Productive Inflammation, Ulceration, and Suppuration."

We must, however, here point out that **regenerative processes** are sometimes discoverable in the cells of an inflamed area, as the following experiment shows:

When Senftleben with chloride of zinc destroyed all cells in the centre of a cornea without admitting any white corpuscles to the area, the part remained quite clear. On the third day microscopic examination showed that the corneal corpuscles around the damaged area were shooting processes into it; nuclei appeared on the processes, protoplasm collected around them, and branched cells formed, which again threw out regenerative processes; and thus the corneal corpuscles were completely restored. Had leucocytes been admitted to the corneal tissue, controversy would have arisen as to whether they also did not spring from the cells by multiplication, but inflammatory phenomena being prevented, the regenerative processes could be studied alone. In other tissues also regenerative processes occur—the more resistant elements endeavoring to make good the loss sustained by the tissue—but such attempts are found only in chronic and subsiding inflammations. In these we must be prepared to find evidence of cell-multiplication, but *not* as a part of the process of inflammation. Injury which causes and fosters the latter tends to prevent the occurrence of regeneration; the more intense the inflammation, the less likely is evidence of regeneration to be found.

THE ESSENTIAL LESION OF INFLAMMATION.—Having thus briefly described the succession of changes which occur in the process of inflammation, we may next consider how an injury can produce them. It has been held to cause abnormal conditions of the blood, of the tissues, of the nerves, and of the blood-vessels. On one or other or all of these parts it necessarily must act.

Lister[1] showed that an irritant did not act through the **blood**, for momentary approximation of a hot iron could affect but a very small quantity of this fluid. Moreover, we can see the circulation going on normally round a microscopic inflammation, whilst corpuscles entering this region tend to stick to each other and to the vessel-walls (p. 246); but if they get through the part they go on toward the heart quite normally. Further, blood drawn from an inflamed area behaves exactly like that from other parts.

The **tissue-elements** are certainly affected in cases due to obvious external injury, but Cohnheim endeavored to injure the vessels only by rendering a part anæmic, washing out its vessels with irritating solutions, and then allowing blood again to flow through the part; when all the phenomena of inflammation ensued. It is therefore possible to produce inflammation by injury of the vessels alone if we can be sure that in this experiment the irritant did not pass through to the tissues; on the other hand, Senftleben's experiments on the cornea (p. 252) show that injury of a non-vascular tissue which does not at the same time affect vessels is not followed by the phenomena of inflammation.

Sensory and vaso-motor **nerves** must often be affected by irritants, and no doubt have their share in producing those variations in calibre and flow which often precede the essential phenomena of inflammation. But as all these latter occur with perfect regularity in a part of which everything except the main artery and vein are divided, nerves cannot be regarded as essential to the process.

There remains, then, only the **vessel-wall**. That this is affected is shown by the facts that all the early phenomena of inflammation are vascular; that injury of vessels alone (Cohnheim) causes these phenomena; that injury of tissues alone (Senftleben) does not cause them. Further, Ryneck has shown that stasis may be produced in the frog's web in which milk or defibrinated blood is circulating in place of normal blood; and also that in vessels the vitality of which has been completely destroyed by the injection of metallic poisons no such stasis can be produced. In all spontaneous inflammations the cause is probably carried to the part by the blood, and acts first upon the vessels, later upon the tissues.

Later investigations have therefore confirmed Lister's conclusions in 1858—viz. that the essential lesion of inflammation was a **change in the vessel-wall** resulting from an injury, which increased the friction

[1] "On the Early Stages of Inflammation," *Phil. Trans.*, 1858.

naturally offered to the passage of the blood, and was a step toward death. There is no detectable structural alteration of the vessel, however; so Cohnheim speaks of the change as "**molecular,**" and regards it as possibly chemical in nature. To cover all that we now know of the escape of fluid and corpuscles, it is necessary to assume that the molecular change not only increases the friction between the blood and the vessel-wall, but also that it renders the latter more porous.

Landerer has recently advanced the view that the obstruction in the capillaries is really due to loss of elasticity (owing to injury) by the tissues in which the capillaries are imbedded: he compares the effect of this loss of support to that which results when the media of an artery is paralyzed. But if we understand him rightly this would cause merely dilatation of the vessel, which scarcely seems to meet the case.

EXPLANATION OF THE MICROSCOPIC PHENOMENA OF ADVANCING INFLAMMATION.—When contraction of arterioles is the first effect of an irritant, it is probably due to its action as a direct stimulant of the vessel-wall; but nothing is really known on this point.

Dilatation with acceleration of flow may probably occur in two ways. Irritation of a sensory nerve is well known to cause dilatation of the arterioles in its own area of distribution, but heightened arterial tonus elsewhere. The action of an irritant not sufficiently intense at once to directly affect the vessels will stimulate the sensory nerves and cause this reflex local dilatation. The arterioles dilate, and, the blood-pressure being maintained, admit a larger quantity of blood than normal to their capillaries, which cannot dilate proportionally. The blood-pressure in the capillary areas is, *cæteris paribus*, increased as the cross-section of the supplying arterioles increases. Under these circumstances acceleration of stream will accompany dilatation of vessels. The walls of the latter, being uninjured, may contract after such dilatation. But Cohnheim found that the same phenomena occurred in the frog's tongue after section of everything except the lingual arteries and veins. They are then due, perhaps, to direct action of the irritant upon the local vascular nervous system, by means of which a certain "tone" is imparted to the vessels even after section of the sympathetic. Dilatation of arteries diminishes the resistance, injury of endothelium increases it. If the former is in excess of the latter, the above phenomena will occur. They are not

seen in severe injuries nor from the slow action of croton oil on a part.

Dilatation with Retardation of Flow.—Retardation soon follows upon acceleration, though the driving force continues unaltered and no contraction of vessels has occurred. Almost the only conceivable cause of slowing is, therefore, increased local resistance due to alteration in the vessel-wall. It is one of the results of the **molecular change.** Resistance, and therefore retardation, increases with the alteration of vessel-wall until **stasis** and even **thrombosis** are reached, the latter, in the case of capillaries, probably implying death of the part.

Escape of Contents of Vessels.—Normally, the vessels permit the escape of the constituents of healthy lymph, cerebro-spinal fluid, the fluid which moistens the pleura, etc. These differ from each other markedly, and we do not know why; but directly an inflammation sets in the normal fluid of the part is changed in proportion to the intensity of the process (p. 251), the quantity of albumen rises, the tendency to coagulate increases, white corpuscles appear in increasing numbers; red are found in the exudation still later, and are in great excess in the most severe forms of the disease. All this is attributed to the **molecular change,** which renders the passage out of albuminous (colloid) bodies more easy, as has been shown by injecting solutions of such bodies, though the vessels bore the normal blood-pressure without bursting, even after red corspucles had escaped.

The plasmatic zone is normally present; heavy particles are drawn into and carried along by the swift, axial stream. It has been shown that when the particles in such a stream are of different weights there is a tendency for the lighter to be thrown toward the circumference, and the leucocytes, being lighter than the red corpuscles, are consequently thrown now and again out of the axial stream into the plasmatic zone, especially in the slower parts of the current (veins). With regard to the **migration** or **diapedesis** of corpuscles, the words are ill chosen as regards the red corpuscles, which can take no active part in their escape. Moreover, it is plain that the force which drives out the red corpuscles when lying against the vessel-wall will act also upon the similarly situated leucocyte. It was formerly thought that these manifested no signs of activity whilst they were within the vessels, but the observations quoted at p. 247 show that they do. Further, von Recklinghausen has seen a pigment-cell in an adult frog work its way into a capillary and send out processes there: and he

argues from this that a leucocyte can work out; so we must admit that leucocytes are able to do something toward their escape. On the other hand, the most active migration is stopped by compressing the supplying artery. This destroys the plasmatic zone, but numerous leucocytes may already be adherent. It would therefore seem that the corpuscles, and especially the red, having come into close contact with the thinned wall of the dilated vessel, are pressed through it by the intravascular pressure, which now can act only on that part of the corpuscle which is toward the lumen. The form assumed by the escaping leucocytes often suggests that they are pressed out by a fluid which also is escaping. It must not be supposed that they are forced through by *increased* blood-pressure; this is diminished in the veins of an inflamed area in proportion as the circulation is slowed by the unusual resistance which it has had to overcome. Cohnheim uses the term "filtration" to describe the process; he says, "Change of filter means change of filtrate." The practical application of the above is either to lessen arterial pressure in inflamed parts or to counterbalance it by uniform support of the tissues.

Destruction of tissue is due to the damage done to the elements of the part by injury, to abnormal physical and chemical conditions from exudation, to the peptonizing action of organisms, and to imperfect blood-supply in the more advanced stages. It is doubtful whether the leucocytes actually destroy tissue; probably their only function is the removal of parts which are dead.

EXPLANATION OF THE CLINICAL SIGNS OF INFLAMMATION.—These are Redness, Heat, Swelling, Pain, and Impaired Function.

Redness and Heat may be taken together, as depending upon the quantity of blood passing through the part in a unit of time. As a rule, this is greater than normal, the excess being most marked in the early stage of the process, when the part is bright red and hot. Then its vessels are fully dilated and the resistance but little increased. As the resistance grows from more marked molecular change and from pressure of increasing exudation, the quantity of blood passing through the part is diminished. Cohnheim measured the blood returning through both femoral veins after inflammation had been excited in one foot of a dog. At first the delivery on the injured side was excessive, sometimes more than twice normal, but when diffuse suppuration or sloughing was induced the delivery became markedly less

than normal. Coldness must go with such a state of matters, and the part will be bluish if its vessels are dilated and full, but mottled or pale if they are compressed by exudation. In most inflammations the internal and external resistances to the circulation are not sufficient to counterbalance the effect of dilatation, and the blood-pressure is kept up; consequently, the delivery from the veins remains excessive throughout and the part is red and hot. Both redness and heat may be concealed by thickness of normal tissues over the inflamed part. An inflamed foot may be several degrees hotter than its fellow, but it is never so hot as the rectum: an inflamed pleura is never hotter than its fellow, but may be colder. The rise of temperature is due merely to more rapid circulation of arterial blood: excess of heat is not produced in the part. Increased nutritive exchange is required to produce heat; depression of function, degeneration, death, and absorption have not this effect. The most recent and exact thermo-electric measurements by Jacobson and Bernhardt are in accordance with this view.

Swelling, beyond the most trivial due to dilated vessels, arises from exudation of fluid and corpuscles. It may be entirely owing to fluid, as in hydrocele, or entirely owing to small round cells, the fluid having been absorbed, as in orchitis. It varies in amount with the distensibility of the part, being most marked in such as the scrotum and eyelids, least so in bone. When due to fluid (*œdema*) the affected part "pits," unless it is very tensely stretched. Swelling from cell-infiltration is firm, does not pit, and is sometimes called "solid œdema." Swelling may be absent in cases of slight inflammation, in which the lymphatics suffice to carry away the increased exudation.

Pain is due to pressure of the effusion on nerve-endings, perhaps also to chemical irritation of them. It is greater the more sensitive and the more rigid the part and the more rapid the effusion into it, as is seen in acute suppuration in a digital tendon-sheath. It is often throbbing from the increase of tension with each heart-stroke. The effect of pressure in producing pain is well shown by allowing an inflamed part to hang down.

Impaired function is due to the fact that every tissue is injured by inflammation.

VARIETIES[1] OF INFLAMMATION.—The process of inflammation is always that which has been described on pp. 245–253, no

[1] Perhaps "degrees" would be a better term.

matter what injury may have been its cause, but we find, both experimentally and clinically, that the exudations produced by injuries of different intensity acting for different periods of time vary sufficiently to allow of a useful classification upon this basis. It will be remembered that the first effect of injury as regards exudation was to increase the quantity of fluid which escaped from the vessels and to render it more albuminous; then, whilst the rise in quantity of albuminous constituents continued, leucocytes appeared in increasing numbers and the fluid became more and more coagulable; with the leucocytes came a few red corpuscles, and these in the most intense inflammations were vastly in excess of the white. These differences in the exudation may be found in passing from the spreading edge toward the centre of an inflammation, such as that which constitutes spreading traumatic gangrene. There is no break in the continuity of its production; the passage from serous to hemorrhagic occurs gradually and *pari passu* with increasing intensity of the injury. Consequently, the following "varieties" are to be regarded simply as steps in the process of inflammation due to variations in (1) the resisting power of the tissues, (2) the intensity of the cause, and (3) the duration of its action.

Serous Inflammation.—As a result of *slight* injury the normal transudation from the vessels is increased in quantity and contains excess of albumen, but very few leucocytes. Consequently, it does not coagulate or only a few flakes form. The best examples are chronic effusions into serous cavities—the pleura, joints, or tunica vaginalis (hydrocele). An effusion of the same kind occurs also in the substance of a part, constituting "inflammatory œdema." Such a part is swollen, "pits" on pressure (unless very tense), and the tissue is found to contain excess of fluid. In impoverished states of the blood, especially when the albumen is diminished, inflammatory exudations, even when the process is of considerable intensity, are liable to be serous. In more intense inflammations also, where the emigration of blood-corpuscles is not fully established, as in the earlier stages of the process, and when the injury to the vessels, although severe, is rapid and transient in its action, as that caused by heat and blistering agents, the effusion is often a clear and only slightly coagulable liquid. With more severe damage the percentages of albumen, fibrinogen, and white corpuscles increase, and fibrin forms in increasing quantity. Networks of fibrin are frequent in the meshes of inflamed connective tissue, and large flakes of it may come away in

otherwise serous effusions. These inflammations are called **sero-fibrinous,** and lead on to the next class.

FIBRINOUS INFLAMMATION.—In this form the exudation is still more richly albuminous and contains more leucocytes; it consequently has a much greater tendency to coagulate, and "**lymph**" forms on the inflamed surface or in the substance of the inflamed tissue. The proportion of fluid to lymph present in the inflamed part should be small to justify this name. The most typical examples are found on serous membranes. On the surface of the visceral pleura, for example, an irritant produces redness from dilatation of vessels; then follows exudation of fluid and leucocytes, and fibrin forms upon the surface, entangling leucocytes in its meshes. Fibrin containing leucocytes constitutes "lymph;" the white corpuscles may be very numerous, or but few may be distinguishable in a granular or obscurely fibrillated matrix. Lymph may now form upon the opposed surface of the parietal pleura, which becomes infected from the original focus, and the two patches blend. This is the first stage in the formation of an "adhesion"—*i. e.* a band of connective tissue between the two surfaces. Lymph, formed in exactly the same way, is the temporary uniting medium in healing by the first intention, and it is similar lymph which "glazes" the surface of an open wound a few hours after its infliction. In these cases the fluid escapes from the free surface. A similar exudation occurs into connective tissue as a result of chronic slight irritation; the fluid is apparently absorbed as fast as it escapes; fibrin probably forms, but is soon removed by the agency of leucocytes which crowd the tissue and replace those parts of it which have been destroyed by the primary injury and the process excited by it. Such an inflammation may end in absorption, some leucocytes wandering into lymphatics and re-entering the circulation; others, together with the fibrin, undergoing fatty changes and forming an emulsion which is similarly absorbed.

PRODUCTIVE INFLAMMATION.—In many cases the inflammatory process ends in the formation of new tissue—inflammatory connective tissue; and the inflammation is then said to be **productive.** In this case any fibrin present disappears before the leucocytes which crowd into the lymph and convert it into a tissue of closely-packed leucocytes in a scanty homogeneous matrix. To supply this with nourishment vascular loops spring from the capillaries of the inflamed tissue and penetrate into the lymph in all directions; this is **granulation-tissue,** the presence of vessels and of a homogeneous instead of a

fibrinous matrix constituting the difference between it and lymph. It derives its name from the fact that on the floor of a healing ulcer, which consists of this tissue, the young cells mass themselves round the apices of capillary loops, all of which project toward the surface; and we thus get the floor made up of rounded projections about the size of a pin's head, which are called "granulations." (See Fig. 87.) *The plentiful formation of vessels is essential to the changes which this tissue undergoes in the production of connective tissue.* In healing wounds new vessels have been found protruding from adjacent capillaries by the end of the second day (Wywodzoff).

The development of granulation-tissue into connective tissue has been studied by Ziegler, who placed chambers formed of two slightly separated cover-glasses in the subcutaneous tissue of dogs, and removed them at varying periods. Up to the fifth day they contained round cells—some with one, others with a bi- or tri-partite nucleus; then there appeared cells twice the size of leucocytes, containing a large vesicular nucleus, slightly contractile and capable of taking particles into their substance. These are often called **epithelioid**—a bad name. Ziegler speaks of them as **formative cells** or **fibroblasts**, because from them all new connetive tissue develops. As they increase in number those with divided nuclei disappear, so it is probable that the fibroblasts feed upon degenerating leucocytes. After the twelfth day giant-cells in increasing numbers were found, formed apparently at the expense of cells in their neighborhood, either by their coalescence or by their degeneration and absorption by a single

FIG 85.

Varieties of New Growth resulting from Chronic Inflammation of Connective Tissue: *A*, an adenoid, *B*, a fibroid, structure. × 200.

cell. Many giant-cells degenerate, but some may develop into connective tissue. This tissue is thus formed: the fibroblasts assume very various shapes—pyriform, spindle, and branched—and are closely

packed in a homogeneous intercellular substance. The protoplasm of many cells on the sides of the nucleus and in the processes fibrillates, and by the union of bundles from different cells and by spread of the process to the intercellular substance we get wavy, intercrossing fasciculi of fibres, to which adhere some of the nuclei of the original cells with a little protoplasm (Fig. 85).

This new connective tissue is called inflammatory or **scar-tissue.** At first it is highly vascular, a recent scar being redder than the surrounding parts; but the tendency to contract is characteristic of this new fibrous tissue, and as this proceeds vessels disappear, and the scar, in the course of some weeks or months, becomes white as compared with surrounding parts. This contraction of scar-tissue may produce most serious results, such as the gravest deformities or atrophy of the essential epithelial elements of glands. (See "Interstitial Nephritis" and "Cirrhosis of the Liver.") It is most marked where the tissues are loose, as about the scrotum; and it appears to be essential to the process of healing, which ceases in a callous ulcer of the leg so soon as infiltration of surrounding tissues and adhesion to deeper parts arrests contraction. A scar is always a weak point in the system, and a tight scar is always irritable and very liable to break down.

But granulation-tissue frequently does not develop into scar-tissue. Continuance of excessive irritation, insufficient development of vessels, diminution of their lumina (as occur in gummata), too dense packing of the cells, and therefore excessive pressure on the vessels, will inevitably lead to degeneration. It has been found that imperfect blood-supply is accompanied by the development of giant-cells; they are found in all truly chronic inflammations. Thus, the typical structure of a tubercle is a giant-cell in the centre, surrounded by formative (epithelioid) cells, whilst outside these is a ring of ordinary leucocytes. In gummata, lupoid nodules, etc. similar structures are frequent. A section through the thickened synovial membrane in a case of chronic arthritis often shows the following appearances: Externally, we find ordinary granulation-tissue, perhaps developing into scar-tissue; passing toward the joint-cavity, we find next a layer of formative cells in which giant-cells become increasingly numerous and typical "tubercles" may occur; yellow spots and patches of fatty degeneration now become frequent, and the surface may be composed of granular débris in which cell-forms are no longer distinguishable. A fluid looking like thinnish pus may occupy the cavity; it contains,

however, but few pus-cells, consisting really of fatty granules, formed by degeneration of the superficial cells, suspended in fluid. This is **chronic "suppuration"** in the knee, and **chronic "abscesses"** of similar nature may form elsewhere, especially in connection with bone (caries of vertebræ, etc.). When starting from bone the puriform fluid formed by degeneration of the granulation-tissue simply distends the tissues round about and forms a bag of them, the wall of which yields little pus. On the other hand, excessive irritation or rise in intensity of the original irritation will destroy some of the cells of the granulation-tissue, and will produce inflammation of it with free escape of corpuscles from its vessels—will cause it, in fact, to "break down into pus." This is best seen when a healing aseptic ulcer, having a serous discharge only, becomes septic; the discharge becomes purulent.

Interstitial is the term applied to inflammations of solid organs of which the manifestations lie chiefly in the connective tissue between the essential elements of an organ; they may be acute, running on even to suppuration, but as a rule they are ordinary productive inflammations—more or less marked secondary changes in the essential cells from interference with their nutrition being constant. In **parenchymatous** inflammations the epithelial elements of the organ show the most marked changes, becoming swollen, finely granular, or even structureless and incapable of staining. These are probably of a degenerative and necrotic nature, mixed up with regenerative processes. (See "Cloudy Swelling.") The essential lesion of the inflammation must, of course, be of the vessels in the connective tissue; but the essential cells of an organ are much more delicate than those of its connective tissue, and show quickly the effects of a strong irritant, which causes engorgement of the vessels of the connective tissue and free escape of cells and fluid into intercellular and intraglandular spaces. Under slight chronic irritants exudation is slow, leucocytes form scar-tissue, and the nutrition of the essential cells is more slowly, but none the less surely, interfered with.

Suppurative Inflammation.—This is a very common form. In it the exudation contains the same elements as in the fibrinous form: the peculiarity of the process is that no coagulation occurs and no lymph forms and vascularizes; even lymph which may have formed at an earlier stage of the inflammation is destroyed when suppuration sets in. The irritant is more intense than that required to produce

(at least some) fibrinous inflammations, and it is essential that its action be prolonged. Serous and fibrinous stages often precede the suppurative, showing that they are minor grades of the process.

Suppuration may be either **acute** or **chronic**: with the latter we have already dealt above. Either of these may appear in a *circumscribed* (**abscess**) or *diffuse form in the substance of a part*, or its seat may be a *free surface*—mucous membrane or skin. In the latter case, when the epithelium is destroyed with more or less of the subjacent tissues, the process is called **ulceration**; but where the deeper layers of the epithelium remain it is a **purulent catarrh.**

Formation of an Acute Abscess.—When we come to consider the etiology of acute suppuration, we shall find that in all probability it is always due to the action upon the tissues of organisms—most commonly the Staphylococcus pyogenes aureus. Some of these organisms become arrested in the capillaries of a part, and *if the conditions are suitable for their growth* they proceed to multiply and to give off the product of their metabolism. All round about them a clear hyaline ring, which does not stain and in which all structure is lost, appears—obviously some irritant, soaking from the cocci into the tissues, has destroyed the latter and they have undergone coagulation-necrosis. In the course of a few hours a ring of leucocytes appears round this area and becomes increasingly dense: they infiltrate the necrosed area and press in toward the centre, whilst the cocci, on the other hand, multiply and pass out. They penetrate the tissue in all directions, lying especially in lymph-spaces, and everywhere the layer of leucocytes is formed to oppose them—at first in vain; but after many have been destroyed and have undergone necrosis the layer of leucocytes becomes so dense that its resistance to invasion is successful, and by degrees the cocci are completely walled in, granulation-tissue everywhere intervening between them and the healthy tissues. In rabbits, after injection of cocci subcutaneously, this limitation begins on the third or fourth day, but is not complete on the average till the ninth: in man it usually occurs more steadily. At first a central yellowish mass of necrosed tissue infiltrated with cocci and leucocytes is found, surrounded by the layer in which cocci and leucocytes are struggling for the mastery. Gradually the central mass softens, and it is noticed that the tissue-elements swell up and become indistinct as the cocci spread among them; moreover, no fibrin forms in the fluid exudation. All this is attributed to a peptonizing action of the cocci which has been shown

to be energetic. No new vessels form so long as the process is actively spreading, but so soon as the leucocytes have got the upper hand they become vascularized into a layer of "granulation tissue." Thus is formed a cavity, bordered by still living infiltrated-tissue, which contains dead leucocytes, fluid intercellular substance and exudation, and a few living cells which have recently migrated from the living tissues. By thrombosis of vessels and molecular disintegration of the cells they supply, by migration of corpuscles and exudation of fluid into the newly-formed space, the process spreads, and always in the direction of least resistance—generally toward some free surface, upon which the abscess bursts. We should find on section of the wall of a spreading abscess all the stages of inflammation —a proof of the prolonged action of the cause. In the centre necrosis, and in succession as we pass outward from this thrombosis, stasis, retardation of flow—diminishing, and perhaps giving place to acceleration, before the normal circulation is reached. With hyperæmia exudation increases; much of the fluid is taken off by lymphatics, but the corpuscles accumulate in increasing numbers, and red join the white outside the vessels as the centre is approached. This account explains how it is that we are led to the belief that suppuration has occurred when over a deep-seated swelling we find developing redness, heat, and œdema—signs of an advancing inflammation.

An acute abscess almost always extends until it bursts or is opened; then tension, a great cause of the continuance of the inflammation, is relieved, and the pus formed escapes together with its original cause. If the cavity is completely drained and kept at rest, and putrefaction of the discharges is prevented, all pus-formation ceases, the round-celled infiltration of the walls speedily vascularizes—if this has not occurred before—and they become lined by granulation-tissue. This grows and blends across the cavity, which is perhaps rendered potential by falling together of the walls; and then it develops into scar-tissue, and thus the abscess is healed.

Pyogenic cocci can enter the skin by the orifices of ducts or through small abrasions. Impetigo results from their penetration into the ducts and multiplication there without penetration of the true skin. If the cocci penetrate to the depths of a hair-follicle or sweat-gland, their action is more violent (greater tension?), and they produce a slough: a boil results. Lastly, if the cocci penetrate the cutis vera they cause an abscess of the skin.

Diffuse suppuration is exactly the same process going on over a wide area. It is often more intense than when circumscribed, and it is by no means uncommon to find shreddy sloughs in the pus, molecular death having been the effect of the injury on some portions of tissue. It is due to the Streptococcus pyogenes, an organism of which the peptonizing power is more intense than that of the Staphylococcus, which possibly accounts for the difference in their action.

Pus from a person healthy but for a simple abscess (*laudable* pus) is a thick, creamy, opaque, yellow-white fluid, slightly viscid, having a faint odor, alkaline reaction, and specific gravity 1030–1033. It contains 10–15 per cent. of solid matter, of which two-thirds are albumen, and the rest fatty matter and salts, such as are found in blood. On standing it separates into a dense yellow layer, *pus-corpuscles*, and a clear supernatant fluid, *liquor puris*.

Pus-corpuscles are spherical bodies about $\frac{1}{2500}$ inch in diameter, semi-transparent, more or less granular, motionless, and usually containing a bi- or tri-partite nucleus, the segments of which together are no larger than the original nucleus. Such division is therefore regarded as evidence of degeneration rather than of multiplication and of growth.

But a small minority of the cells have exactly the appearance of leucocytes and perform amœboid movements. These are the more recently escaped cells. Acetic acid clears up the cells, and renders obvious the often obscure nucleus (Fig. 86).

FIG. 86.

Pus-corpuscles as seen after Death: *a*, before, *b*, after, the addition of dilute acetic acid. × 400.

It is noteworthy that pus has no power of absorbing sloughs or sequestra; *living* cells are required for this. A bit of bone, even an ivory peg, surrounded by granulation-tissue will be slowly eroded, but it may be in pus for months without losing weight, and suppuration is not likely to cease until it is removed. The prevention of suppuration is therefore to be aimed at in all cases of necrosis and of retention of foreign bodies (especially absorbable ligatures) in wounds.

Terminations of Acute Abscess.—Sometimes, though rarely in the case of an acute abscess, after some pus has formed the irritation becomes so slight that granulation-tissue forms round the fluid and develops into fibrous tissue. The pus may long remain encapsuled, its corpuscles breaking down into fatty débris; but as a rule the fluid part is absorbed, and a more or less dry, cheesy-looking mass, con-

sisting of cell-débris and cholesterin crystals, is left in the capsule. The mass may calcify. Such collections may lie harmless in the tissues for years, and finally become the centres of fresh suppuration. These changes are much more common in chronic abscesses.

Ulcerative Inflammation.—We have seen that suppuration in the substance of tissues produces molecular disintegration of them; as a rule, no distinct slough is found in pus. The same molecular destruction eating away the tissues on a free surface constitutes ulceration. Under the action of an irritant the superficial layer of the skin becomes soaked with fluid, and leucocytes escape in numbers from the vessels and wander even into the epithelial cells, where they seem to have arisen by endogenous multiplication. Under these circumstances the superficial cells do not become horny, and are easily brushed off, or the original irritant may have destroyed their vitality and cohesion, and they are washed away by escaping fluid. The rete is now exposed, and irritation of the deeper tissues by slight friction, contact with chemical irritants, putrid discharges, etc. is easy. The inflammatory process becomes more intense, the escape of fluid and leucocytes freer, and stasis and thrombosis occur here and there. Death of portions of the papillary layer and of the covering epithelium follows; they disintegrate rapidly and come away in the discharge. The process spreads by the production of limited stasis and death of tissue; if the stasis is at all widespread, a visible slough will result. It is common, indeed, to see tags of dead tissue adherent to the floor of a spreading ulcer; more intense irritation will at any time time render them larger—transform them into "sloughs." Ulceration passes insensibly into gangrene as death becomes too rapid to permit molecular disintegration of the dead parts as they form by degeneration and the action of leucocytes. The discharge in the spreading stage consists of a few leucocytes and débris of broken-down tissue suspended in fluid. Like the edge of advancing suppuration, the margin of a spreading ulcer exhibits all the stages of inflammation from the mildest to the production of molecular death. An abscess is often described as a closed ulcer. When the causes of the inflammation are removed, the round-celled infiltration of the floor increases and becomes vascularized into granulation-tissue (Fig. 87). Sloughs are thrown off by the eating through of their connections with living parts, and soon the base becomes covered with "granulations." When healthy, these are bright-red, slightly raised, rounded elevations, about the size of a small pin's head, and consist of cells grouped round a

capillary loop. They contain no lymphatics and no nerves, and are not tender and do not bleed readily. Departure from this type indicates disease of the granulations.

FIG. 87.

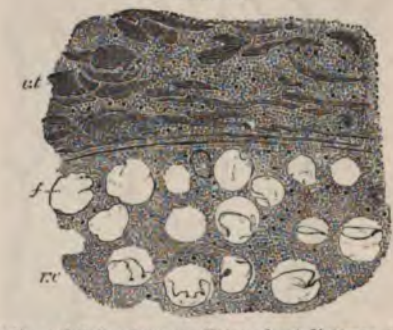
A Granulating Surface: *a*. Layer of pus. *b*. Granulation-tissue with loops of blood-vessels. *c*. Commencing development of the granulation-tissue into a fibrillated structure. × 200. (Rindfleisch.)

The granulation-tissue grows either by multiplication of its cells, or, as some think, by vascularization of leucocytes which continue to escape from the newly-formed vessels under the irritation of exposure, dressings, etc.; and it replaces such loss of tissue as has occurred. At the same time all infiltration is removed from the edges, and they sink gradually into the base. Epithelium now shoots in from the epithelial cells at the margin, and three zones can often be distinguished here—an inner, dry, red zone, where the cells are one or two thick; then a wider blue zone, where they are thicker, but where no horny cells exist; and lastly, an opaque white ring of sodden, horny epithelium. The deeper layers of the granulation-tissue are meanwhile becoming scar-tissue, contracting and drawing together the edges of the sore, so the epithelium has less and less to cover; and finally the

whole surface is skinned over and all granulation-tissue is converted into fibrous tissue. Contraction goes on even after this, and the resulting scar is very much smaller than the original ulcer.

HEMORRHAGIC INFLAMMATION.—This form of inflammation is characterized by an exudation in which red corpuscles are in great excess. Red corpuscles are the latest to escape of the contents of vessels which we can watch whilst they are subjected to the action of an irritant. In a case of spreading traumatic gangrene under the care of Mr. Boyd the tissues a short distance above the actually gangrenous part were crammed with red corpuscles, showing that the vessels could hold none of their contents (Fig. 88); higher up there was a free escape of

FIG. 88.



Deeper Layer of Cutis and Subcutaneous Fat a short distance above the Dead Part in a Case of Spreading Gangrene: The interstices of the tissues are crammed with red corpuscles and a few white. *c.t.* Connective tissue; *f.* fat-cells; *r.c.* red corpuscles. × 200.

leucocytes and of a sero-fibrinous effusion (Fig. 84); and higher still was effusion of simple serous fluid. Of course the injury may be so intense as to cause free escape of red corpuscles from the capillaries at once. The fluid which soaks the part in these cases is usually thin and more or less deeply blood-stained. The greater the number of capillaries present in a tissue, the more likely is an exudation to be hemorrhagic; severity of injury is the other factor. There are generally many red corpuscles present in the exudation of acute pneumonia. The free escape of red corpuscles shows that the capillary stream in the part is reduced to a minimum, that the injury done to the tissue is a very grave one, and that stasis, death, and thrombosis are impending. Too often obvious gangrene is the termination of such inflammation.

TERMINATIONS OF INFLAMMATION.—I. Resolution.—

This, the most frequent and most favorable termination of inflammation, consists in the cessation of the process and the restoration of the part to health. For this to occur it is necessary, first, that the exciting cause be removed; next, that the walls of the blood-vessels be restored to their normal condition, in order that abnormal transudation may be arrested; and, lastly, that all exudation be removed and killed or damaged tissue-elements regenerated. This restoration will obviously be more easily effected in the earlier than in the more advanced stages of the inflammatory process. But resolution even of stasis sometimes occurs, and may be watched under the microscope. The corpuscles of the stagnant blood move off, one after another, till a slow stream is re-established through the inflamed area; the flow quickens as resistance lessens and as the vessels contract, owing to gradual recovery of their muscular coats; exudation, first of corpuscles, then of fluid, ceases; and the circulation again becomes normal. Serous, sero-fibrinous, and productive inflammations in their early stages are those which end in resolution; once normal tissue has been replaced by granulation-tissue or scar-tissue or has been destroyed by suppuration, ulceration, or gangrene, resolution is impossible. A normal condition of the walls of the blood-vessels is dependent upon the proper circulation of the blood through them and the vasa vasorum. Whatever, therefore, favors the re-establishment of normal circulation in the inflamed area will, as pointed out by Cohnheim, favor resolution.

The last element in resolution is the removal of the inflammatory products—fluid and corpuscles. These are removed mainly by the lymphatics, but after restoration of the circulation absorption is carried on to some extent by the veins also. In the later stages of the process any unabsorbed blood-corpuscles or fibrin undergoes fatty degeneration, and thus the complete removal of the inflammatory products is much facilitated. (See "Gray Hepatization.") The process of regeneration in the various tissues has already been described.

All conditions interfering with the lymphatic or vascular circulation, such as the pressure exercised by a large effusion in a serous cavity or by a richly cellular exudation in a lymphatic gland, must retard resolution. (See "Caseation" and "Scrofulous Inflammation.") Interference with the lymphatic circulation tends especially to prevent absorption—interference with the circulation in the blood-vessels to prevent that restoration of those vessels to a normal condition which is necessary to arrest the continued transudation.

II. **Necrosis.** — Inflammation may terminate in death of the inflamed tissue. Inasmuch as inflammation is always due to injury, the process is probably accompanied, in all but its slightest forms, by death of tissue-elements (Weigert); careful microscopic examination may be necessary to detect this. Clinically, we do not speak of necrosis unless obvious death of tissue has occurred, and generally *en masse* (gangrene), as distinguished from the molecular destruction characteristic of suppuration and ulceration.

The more severe the injury, the longer its period of action, and the feebler the resistance of the tissues, the more likely is necrosis to result. It may be produced in the following ways:

1. By severe injury acting on a part, not killing it at once, but by continued action producing inflammatory disturbance of the circulation, ending in thrombosis. The tissues are affected by the injury equally with the vessels, and suffer also from the circulatory disturbances.

2. By an irritant conveyed to the part by the vessels, affecting them primarily and inducing the above changes in them. The tissues are affected secondarily both by the irritant and by the circulatory disturbance.

3. By pressure of inflammatory exudation, fluid or solid, rapidly or slowly strangulating the supplying vessels; as in sloughing of skin from tense œdema, necrosis of tendons in whitlow, death and degeneration of cells in chronic inflammations. Death is more likely to be produced in this way when the exudation occurs in unyielding parts, especially into bone: here death of the exudation before the bone is completely eroded means death of the bone and formation of a sequestrum.

In all infective inflammations the irritant exercises its deleterious effect upon the cells of the inflammatory exudation and tends to destroy them.

Some causes of inflammation always lead to gangrene—*e. g.* those of carbuncle, malignant pustule, hospital gangrene. Such inflammations are sometimes called **gangrenous** or **necrotic.**

The ulcerative process by which a slough or sequestrum is detached has already been described (p. 42).

The **diphtheritic** is a special variety of necrotic inflammation. It affects the surfaces of mucous membranes and wounds. It finds its type in the inflammation of the pharynx and adjacent parts, which characterizes the disease "diphtheria." In this the affected mucous

membrane is covered by a more or less firmly adherent "false membrane," of gray or yellow color (sometimes looking like clot from presence of red corpuscles), generally rather tough, but sometimes quite pulpy. Microscopically, it seems to consist of a close network of fibrin, containing here and there leucocytes in the meshes; but the deeper part of the membrane consists of what look like flakes of coagulated albumen. The epithelium is completely destroyed, together with more or less of the subepithelial tissue. These false membranes, however, resist much more strongly than fibrin the action of reagents—*e. g.* acetic acid; and Weigert states that they are formed by "coagulation-necrosis" of the epithelial and connective-tissue elements. Certain of these cells are killed by the injury, and Cohnheim (adopting Schmidt's views of coagulation, p. 213) suggested that in dying they gave origin to a ferment and to a body like paraglobulin, which united with the fibrinogen of lymph—a hypothesis supported by the fact that the diphtheritic process occurs only in parts freely supplied with lymph, and is arrested by suppuration as the formation of fibrin is. When affecting only the epithelial layer of the larynx the disease is called "croup;" so the distinction between the *pathological* terms "croup" and "diphtheria," though arbitrary, is clear.

A similar pathological change may occur on any mucous membrane—*e. g.* conjunctival (diphtheritic conjunctivitis), intestinal (dysentery). These are infective inflammations, but simple injuries, like scalds, will produce the same anatomical lesion. The existence of a "diphtheritic" (pathological term) membrane by no means implies the poison of diphtheria (clinical term) as its cause.

Such membranes must be distinguished from those formed of lymph—*i. e.* fibrin with entangled corpuscles.

III. **New Growth.**—Inflammations ending in new growth are the so-called "productive" inflammations (p. 259). For this to occur the inflammation must reach the fibrinous stage, it must endure for some time, it must not pass on to suppuration, and the blood-supply must be plentiful.

ETIOLOGY OF INFLAMMATION.—Clinical observation has shown that certain inflammations appear to have obvious causes, such as blows and strains: these are called **simple, traumatic,** or **phanerogenetic.** We shall presently see how few inflammations fall entirely under this heading. In the vast majority of instances no cause is obvious: these may be called **cryptogenetic,** although of late years

the causes of many such inflammations have been clearly demonstrated.

It must always be rememembered, in considering the mode of production of an inflammation, that *there are two factors in the process*—**the cause** and **the tissues** upon which it acts. As in the case of other morbid conditions, the causes of inflammation are **exciting** and **predisposing**: sometimes no predisposition is necessary, but often the exciting cause of an inflammation cannot act unless the resisting power of the tissues to the irritant in question has been lowered. This impairment of resisting power is the work of the "predisposing" causes; and it may be either inherited or acquired (p. 30). It is obvious that in cases where predisposition is necessary the condition of the tissues is as essential to the production of an inflammation as is the presence of the exciting cause: the seed and the *suitable* soil must come together to produce the plant.

With regard to the nature of the exciting cause, it is always some mechanical, chemical, or physical agency, or the simple withholding of food, which injures the vessel-walls and the surrounding tissues. These agents, if of sufficient strength and continued for a sufficient time, would cause death of the part; short of this, they produce distinct changes toward death (p. 250), and in their slightest intensity they act as simple "depressants"—*i. e.* predisposing causes of disease. Every condition opposed to the health of the whole or of part of the body will here find its place.

Difficult as it is to discover the cause of many inflammations, we should bear in mind the very obvious fact that *no inflammation ever arises without a cause or causes. If an inflammation spreads, its cause has spread before it;* and *persistence of an inflammation* (chronicity) *implies continued action of its cause.*

I. Simple, Traumatic, or Phanerogenetic Inflammation.—These are due to the action of some obvious injurious agency, such as mechanical violence, the action of caustic and irritant chemicals, of excessive heat or cold, of electricity strong enough to produce electrolysis of the fluids of the part, or of prolonged local anæmia and consequent privation of blood. It is characteristic of inflammation from these causes alone that it has *no tendency to spread beyond the part originally injured, nor to pass on to more advanced stages after the cause has ceased to act.* Every one knows how slight are the inflammatory changes induced by very severe subcutaneous injuries, smashing bones, opening up joints, etc.; and it is to be hoped that

all will soon be equally familiar with the absence of inflammation when similar but compound injuries are treated in such a way (antiseptically) as to exclude all secondary causes. In animals the effects of each of these irritants can be exactly studied. Hüter injected a 5 per cent. solution of nitrate of silver or of chloride of zinc into muscles and other tissues of animals, quite killing the part acted on. In a large number of the cases no sign of inflammation was found in the surrounding tissues. Other experiments were made by plunging a cautery into a muscle (Hallbauer) and bringing the previously divided skin together over the injured part, antiseptics being used. Only such changes occurred round the eschar as take place in the absorption and replacement by fibrous tissue of a simple infarct. Here, then, we have examples of the most severe mechanical, chemical, and physical injuries killing considerable massss of tissue, and yet inflammation does not advance beyond its earliest stages. In each case the irritant, though intense, is fairly localized in its action, which is of short duration. Certain parts are absolutely killed by it, and the area around these, which is damaged, is a very narrow one. So soon as the noxa has ceased acting the tissues tend of themselves to recover; hence inflammation excited by such causes as the above is at its height very soon after the action of the irritant, and tends soon to subside unless some fresh irritant is introduced. This is frequently seen after the infliction and proper treatment of a clean-cut wound by a sharp knife (p. 119). A chemical irritant may enter the body at a distance from the part at which its chief action takes place; thus alcohol taken by mouth causes cirrhosis of the liver, and turpentine or cantharides inflammation of the kidneys, by which organs these drugs are eliminated.

Under this heading come inflammations which are referred to cold and wet—"rheumatic" and "reflex" inflammations. When a man gets conjunctivitis from the action of a draught through a keyhole upon his eye, the relation between cause and effect is easily comprehensible: except on the hypothesis of greater delicacy of nerve-tissue it is not quite so easy to understand why a neuritis of the facial should ensue from exposure to cold, whilst a great thickness of superficial tissue seems uninjured. But this difficulty becomes much greater when internal organs (lungs, kidneys) become inflamed, apparently in consequence of cold acting upon the surface, of wet feet, etc. Pneumonia, which appeared to be an example of this, seems likely to prove an infective disease. In this case any effect produced by cold can be

regarded only as predisposing. We know that surface cold drives the blood to internal organs and raises the blood-pressure; can this produce inflammation? Lassar plunged rabbits, shorn of fur, into iced water and thoroughly chilled them; he found changes in all the organs, especially the lungs and liver, in which the vessels were often greatly dilated, the arteries thrombosed and patches of round cells lay about the veins: the same changes were noted in fœtal organs when the animals were pregnant. He believed the changes to be due to the irritant action of cooled blood upon the vessels of internal parts. Perhaps something of the same kind may occur in man, and a *locus minoris resistentiæ* must be assumed to explain why the kidney in one case, the lung in another, is affected. Frequent exposure to cold might then well be regarded as a cause of chronic nephritis, for the temporary albuminuria induced in some people by a cold bath shows that the kidneys become much congested.

It is held by some that **excessive functional activity** is a direct cause of inflammation, conjunctivitis from overwork being the usual example.

Nervous influence, too, called into action by irritative lesions of nerve-trunks, is regarded as a direct cause, herpes zoster being the favorite instance out of many which might now be quoted as more or less probable examples. The data are not yet sufficient to decide the question (p. 24).

II. Cryptogenetic Inflammations.—In a very large number of the inflammations met with in practice there has been no obvious mechanical, chemical, or physical injury. Until recently the causes of such were obscure, and they have hence been called **cryptogenetic**, a better name than "idiopathic." In the chapter on Vegetable Parasites evidence is given which proves that some, and renders it probable that all, of these inflammations are due to the action of various fungi. These may act either as mechanical or as chemical irritants; essentially, therefore, they produce inflammation in the same way as do the gross lesions which have been mentioned as causes of simple inflammation. But the living and particulate nature of these poisons confers upon the processes to which they give rise so many peculiarities, besides that of obscurity of origin, that they are best treated of separately.

Fungi by their growth in animal fluids keep up a *continuous* supply of the products of their life-action so long as the conditions are suitable for their development. Different fungi give rise to products vary-

ing enormously in their power of injuring the tissues—some producing actual gangrene, others the various degrees of inflammation in either an acute or chronic form. It is for the production of those forms of inflammation which require the *prolonged* action of an irritant that the fungi are so peculiarly suited; for so long as they can grow, a *continued supply* of irritant is kept up. If the irritant is tolerably intense, some variety of fibrinous inflammation is induced, just as by croton oil (p. 282); but if a strong irritant can also peptonize dead tissue and fibrin, suppuration results. If the irritant is less intense, the early stages of productive inflammation (p. 259) result, as in tubercle, leprosy, farcy. The characteristic lesion of these and some other diseases is a tumor-like inflammatory nodule developed round a spot at which parasites have lodged, and whence they may spread and infect neighboring and distant parts. These lesions are therefore spoken of collectively as the **Infective Granulomata**, a name signifying infective, tumor-like formations of granulation-tissue (Ziegler).

But it would be a very great error to suppose that the **presence of organisms** capable of producing irritant products is sufficient to cause inflammation. We have already pointed out that the **resistance of the tissues** must always be taken into account; and although we are still probably far from knowing all the conditions which influence these two factors—the germ and the soil—experimental pathology has discovered some of them, often of a most astonishing nature. Our knowledge up to date upon this subject has quite recently been ably summarized by Cheyne in his lectures at the College of Surgeons.[1] We shall speak first of the tissues.

1. Arrest of the Organism.—Given an organism capable of inducing inflammation, it obviously cannot act so long as it is moving with the blood: apart from the fact that rest favors the development of bacteria, the organisms must *settle* in a part to irritate it by their products sufficiently to set up an inflammation. Thus, pyogenic cocci have been frequently found in the blood in septicæmia and scarlatina, in the milk of women suffering from puerperal fever, and in the pus of osteomyelitis present at birth—the patient (through whose blood the cocci must have passed), or the mother in the last case, having no abscess. Again, lymphangitis is much rarer than lymphadenitis, because germs are arrested in the filter-like glands, but not so readily in the vessels. Numerous methods have been employed to cause organisms to stick in capillaries which previously allowed them to

[1] *Brit. Med. Journ.*, Feb. 25, 1888.

pass, such as mixing them with sterilized cinnabar or potato starch, the result being impaction of the cocci and development of inflammation, thus demonstrating the effect of simple arrest of the germs. In man this arrest of organisms in circulating blood may be brought about by embolism, thrombosis, or extravasation of blood from injury.

2. **Predisposition.**—Unless, however, the animal is strongly predisposed to suffer from the products of the organisms thus arrested, their impaction in vessels may not be sufficient to enable them to excite inflammation; thus Ribbert found numerous masses of pyogenic cocci in the capillaries of the lung and other organs of rabbits twenty-four hours after their injection, but all disappeared in forty-eight to seventy-two hours, except in the kidneys, where alone abscesses formed. Rabbits are less prone than man to suffer from these organisms; and in them, at all events, and very likely in man also, *the predisposition of the tissues must be increased* before these particular organisms (pyogenic cocci) can excite inflammation. The predisposition to suffer from the attacks of organisms is increased by any *general depression of vitality;* thus, Cheyne sometimes found *living* organisms in the tissues of animals to which large doses of phosphorus had been administered, and states that even certain non-pathogenic organisms may be enabled to live and multiply in the body by the injection with them of a sufficient quantity of the poisonous products of their life-action in a nutrient fluid. It will be inferred that when suspended in water and injected without their products the microbes are destroyed by the tissues before they have time to form enough poison to depress and disable the cells of the body. Similarly, depressed vitality is seen after severe acute fevers in alcoholic, albuminuric, diabetic, and "unhealthy" patients, as compared with the healthy and especially with savage races. Among the latter serious wounds frequently heal by first intention, as among animals. **Local depression of vitality** may be brought about by any kind of injury, and it is here that the "simple" causes of inflammation chiefly come in as predisponents, rendering the tissues more open to the attack of micro-organisms. It has been experimentally demonstrated that anæmia of a part for some hours enables septic cocci to settle and excite a progressive inflammation: the effect of ordinary mechanical injury (*usually slight*) in leading to simple abscess, osteomyelitis, tubercular disease of joints, etc. has long been known, and it has been proved that such lesions act either by simply depressing the ti-

sues or else by causing extravasation of blood, and thus allowing germs which cannot grow in the circulating blood to pass out into the connective tissue, multiply, and excite inflammation: ordinary chemical irritants similarly depress the tissues and excite simple inflammation; and Cheyne points out that strong injections into septic cavities probably facilitate the entry into the body of any organisms which they fail to destroy. The injurious effect upon the tissues of strong cold or heat applied directly to a part needs no comment, and we have (at p. 274) Lassar's experiments showing the effect of cold applied to the surface upon internal organs; and though it is not yet known how the cold acts, we may conclude that it would facilitate the passage of organisms into the tissues of the parts which become interstitially inflamed. These agencies, if they cause recognizable changes, excite some stage of inflammation, and the view that an infective inflammation may, so to speak, be grafted on to a simple inflammation has met with wide acceptance. It would seem, however—contrary to what might, perhaps, have been expected—that pyogenic cocci and other organisms circulating in the blood do not enter the inflamed area and pass out into the damaged tissues in all stages of the inflammatory process: they do so freely until the stage in which leucocytes escape in numbers is reached, when, according to Rinne's experiments, they are not to be found in the vessels of the inflamed area. Cocci injected during the formation of scar-tissue are said to enter the vessels of the damaged part in excessive numbers, and may pass out into the tissues, but when the scar is fully formed no such difference is noticeable. The explanation given of these observations is that in the early stage of inflammation the tissues are weakened by the injury and unable to cope with invading organisms, which consequently multiply in them; but in a more advanced stage, when free escape of leucocytes is occurring, the damaged tissues are infiltrated, and perhaps replaced by a swarm of healthy active cells, which are, as a rule, capable of dealing with pyogenic cocci. Scar-tissue, again, in its early vascular stage seems to be of feeble resisting power. It sounds somewhat strange that the early stage of inflammation should give rise to a *locus minoris resistentiæ* as regards pyogenic cocci, whilst a later stage does not do so; but Cheyne thinks that it fits in well with the fact that acute osteomyelitis and tubercular disease are often induced by slight injuries—rarely by severe, which excite too much reaction. We have probably a good deal yet to learn in the matter.

3. The **seat of inoculation** and the **anatomical arrangement**

of a part also are of importance in enabling organisms to obtain a foothold in the body in two ways; for—1, certain microbes can grow only in certain tissues, and are harmless unless they reach and settle in those tissues; and 2, the physical characters of a part have much to do in determining whether an organism can live there, and what form of inflammation shall result from its action. The bacillus of malignant œdema illustrates both these points: it can grow only in connective tissue: when introduced into the blood it sooner or later dies out, leaving the animal protected against the disease, but if, whilst it is circulating, a bruise is produced, the bacilli pass out with the blood extravasated into the tissues and commence to grow and cause the lesions of the malady. Again, inoculation with this organism at the tip of the tail in cattle has little effect, on account of the density and coldness of the part: the intensity of the disease increases as the point of inoculation approaches the body, and the reaction may be increased also by raising the temperature of the more distal parts. Sheep, which have loose tissue in their tails, react strongly when inoculated even at the distal extremity of this appendage, and the reaction is diminished by cooling the part. Cheyne has shown that the injection of a certain quantity of a cultivation of the Proteus vulgaris into the subcutaneous tissue of the back of a rabbit caused an abscess, but the same quantity in the muscles of the back produced death; and, further, an amount of the cultivation too small to have any appreciable effect in the subcutaneous tissue caused an abscess among the muscles. No explanation is as yet forthcoming. The limitation of acute infective osteomyelitis to growing bones is another example of the influence of structure upon disease; and a last illustration of this point may be found in the difference between the behavior to pyogenic cocci of the peritoneum and the cellular tissue. The success of a surgeon who washes out the peritoneum after operation with ordinary unpurified tap-water has been greater than that of any one practising the most rigid antiseptics: the result of washing out wounds of the soft parts or of bones, on the other hand, is very unfavorable, acute inflammation often supervening after such practice. The explanation given is that the peritoneum has great powers of rapid absorption, so that considerable quantities of putrescible fluids may be injected, together with septic organisms, into its cavity, and they will be completely absorbed before putrefaction has time to advance to a poisonous extent; but if injected in still larger quantity putrefaction occurs with great rapidity in the unabsorbed fluid,

and death from septic intoxication results. The absence of peritonitis is due, according to Grawitz, to the rarity of pyogenic cocci in the air: he says that peritonitis results when pyogenic cocci are present, either alone in too large numbers to be speedily destroyed or along with too much fluid to be rapidly absorbed, or in a peritoneum disabled for rapid absorption by disease. This explanation, however, seems hardly to cover cases of acute peritonitis starting from a small wound, situate perhaps at the lowest point of the cavity, or from a bruised retained testicle; in such instances it would seem as if neither of Grawitz's conditions could be fulfilled. It is notorious, moreover, that a chronically inflamed peritoneum with a good many adhesions about stands injury better than a normal membrane, and we have not seen any proof that the lymph-flow from the former is more free than from the latter.

4. Lastly, the **blood state** in Bright's disease and diabetes is favorable to the growth of the cocci which cause boils and carbuncles; and hydræmia is said to act similarly.

We turn now to the first factor in the etiology of inflammation—

The Bacteria.—We have already (p. 275) pointed out how greatly the process may vary in intensity according to the **species of organism** which gains foothold in the tissues. But even the same organism may be caused to produce very different results according to the way in which it is handled.

I. **The number of organisms** which gain entry to the body at any one time is a matter of great importance. At first sight, one might think that the only difference in the results after the injection of 1 and of 1,000,000 pathogenic microbes would be the somewhat slower development of the disease in the former case; but after it had been found experimentally that this was not so, except in cases of animals strongly predisposed to suffer from the organism in question, it was seen that small numbers of organisms would be destroyed by the tissues before they could produce their products in any quantity, whilst a very large number could not be got rid of with sufficient speed to prevent them from producing more or less poison, and thus gaining a greater or less advantage over the tissues. Upon this point Cheyne's own researches enable him to enunciate the following laws: 1. The pathogenic dose of a virus varies inversely with the predisposition of the animal to the disease in question. 2. In animals not very susceptible to a germ disease the severity of the disease varies directly, within certain limits, with the dose: a small dose

produces no effect, the germs being rapidly destroyed; a larger one causes a local inflammation of greater or less intensity, the organisms being hemmed in and destroyed more or less speedily by leucocytes; whilst a very large dose cannot be thus limited; the organisms penetrate into the circulation, produce poisons freely, and death from septic poisoning results. We cannot with certainty predict the dose necessary to produce any one of the above results, because predisposition varies greatly even among animals of the same species.

II. **The virulence of pathogenic organisms** may usually be increased or diminished ("attenuated") by suitable external conditions; thus, attenuation may result from cultivating an organism and allowing long intervals to elapse between the successive inoculations, by cultivating at a temperature at which growth is very slow or upon media containing antiseptics in quantity not sufficient to inhibit growth. Increased virulence is rarer, but the bacilli of symptomatic anthrax are said to become markedly more virulent after the addition of a little lactic acid and sugar to the culture-soil upon which they are growing. As such slight variations in external conditions as the above can effect such important modifications in these organisms, it is evident that the body may have to deal with them in states of varying virulence: the weaker the virus, the more of it will be required to produce a given effect, and *vice versâ*. The absence of inflammation from wounds treated carelessly or left to nature may sometimes be due to the attenuation of any organisms which have fallen upon it.

III. **Concurrent growth with other bacteria** may either increase or diminish pathogenic action, and many facts make it probable that the presence of putrefactive with pyogenic cocci in a wound considerably increases the danger to the patient; for the putrefactive organisms by their irritant products destroy the granulation-tissue and open up the way of entry for the pyogenic germs. A corresponding fact, vouched for by Cheyne, is that general tuberculosis is much commoner in cases of joint disease complicated with *septic* sinuses than in cases which are kept aseptic. Again, it is said that an osteomyelitis due to a mixed infection of the Staphylococcus aureus and albus is of greater severity and of worse prognosis than a case in which one only of these organisms is present. On the other hand, recent experiments have shown that two microbes growing in the body may successfully oppose each other: to select one of many examples, if erysipelas cocci be injected subcutaneously and into the blood twenty-four hours before infection with anthrax

bacilli, so that a large number of cocci are present at the time of the infection, even a very large number of the anthrax germs may be introduced, and they will die out in seventeen to twenty-four hours without causing even local œdema. Now, these two organisms will grow together readily outside the body, so it is not clear how their opposition in the body is brought about.

IV. Lastly, it is probable that **local** and **seasonal conditions** may act upon pathogenic organisms, and thus account for such peculiarities of disease as endemicity—greater prevalence at certain times and under certain atmospheric conditions.

To summarize this somewhat long account of the factors concerned in the production of inflammation, it would appear that the exciting cause of the great majority of inflammations which are met with clinically is an organism of one kind or another, and this is essential and therefore constant. But in a large number of cases these germs fail to excite any inflammation unless assisted by other conditions, of which the most important seem to be depression of the resisting power of the tissues and a large and concentrated dose of the organisms.

ETIOLOGY OF ACUTE SUPPURATION.—The avoidance of suppuration being of extreme importance to the surgeon, the etiology of this form of inflammation has been studied with extreme care and interest. From what we have said as to the unity of the process of inflammation, it may be thought that the etiology of one of its results required no special investigation; but we have pointed out that, contrary to what we should have expected in an intense inflammation, no formation of fibrin occurs in suppuration; and this peculiarity requires explanation. We may say that a cause of suppuration must (1) act for a sufficient length of time, with (2) sufficient intensity, and (3) must possess the peculiarity of preventing the formation of fibrin. No irritant, no matter what its intensity, causes suppuration if it act only for a short time: neither very slight nor very intense irritants cause suppuration; and, lastly, if fibrin forms and neither it nor the tissue destroyed by the inflammation is dissolved, a necrosed patch, like that resulting from simple embolism, would result. The question whether these requirements can be found among the "simple" causes of inflammation has been much discussed, and many experiments have been made to determine the point. Speaking generally, none of the irritants of this class acting under natural conditions produce suppuration. If intense, the animal soon gets away

from them; whilst those which do not cause pain—*e. g.* a foreign body lodged in the tissues, alcohol taken by mouth, or ordinary cold—are not sufficiently intense to cause suppuration, no matter how they act. But there is still some uncertainty as to whether some simple irritants cannot be so employed experimentally as to yield a different result. Nitrate of silver and similar salts when injected form albuminates, and probably soon cease to irritate; but if glass capsules of croton oil or turpentine, which are not thus neutralized, are placed aseptically in the subcutaneous tissue and the capsules broken when the wound is soundly healed, suppuration results, and no organisms are found in the pus (Cheyne, Councilman).

Strauss, Klemperer, and many other recent observers, on the other hand, using extreme precautions to prevent the entry of organisms along with the needle (*e. g.* cauterization at the point of puncture), have come to the opposite conclusion—viz. that under no conditions do simple chemical irritants give rise to the formation of pus. Cheyne,[1] in summing up the evidence upon the question, concludes that the difference of opinion is due to the fact that the putty-like mass of slowly dissolving dead cells and fibrin which some observers have called pus is not regarded in this light by others; and he agrees that true, creamy pus is never seen in man apart from organisms. He mentions, however, that Grawitz and Scheuerlen have produced acute aseptic (free from organisms) suppuration by the injection of cadaverine and putrescine, alkaloids separated by Brieger from putrid flesh, which are not only irritants, but **also prevent coagulation.** There may be other similar substances.

The conclusion is, that in practical medicine and surgery we do not meet with the formation of true pus as a result of the action of "simple" causes.

Acute suppuration appears to be invariably due to the action of micro-organisms—not of any specific virus, about a dozen "pyogenic" germs being already known. By far the most common of these is the Staphylococcus pyogenes aureus, which grows in bunches, most rapidly above 30° C., liquefies gelatin and produces in it on agar and on potatoes an orange-colored pigment; it peptonizes energetically and lives in the dry state for weeks. Staphylococcus pyogenes albus differs from this in producing no pigment; Cheyne combats the ordinary view that it is less virulent than aureus. The Streptococcus pyogenes grows in chains, often very long, slowly at summer heat, more

[1] *Loc. cit.*

rapidly at the body-temperature; it spreads little on the surface of the culture-ground, forms small white colonies, and does not liquefy gelatin; it peptonizes even more energetically than Staphylococcus aureus, and it is found associated especially with spreading and diffuse suppurations, whilst the staphylococci cause a circumscribed abscess. We may perhaps just allude here to the gonococcus or microbe of gonorrhœa: it causes suppuration of certain mucosæ, but is incapable of producing an abscess in the subcutaneous tissue, disappearing speedily when injected. Gonorrhœal bubo is said to be due, not to the gonococcus, but to a mixed infection with staphylococcus.

Proof that these organisms can cause suppuration has been afforded as follows: Similar operations were performed with antiseptic precautions on both eyes of each of a series of rabbits, and then one eye was infected with pyogenic cocci, chiefly aureus; all the aseptic eyes healed without suppuration; all the infected suppurated and were destroyed, except those in which the operation was superficial (Knapp). Upon man numerous experiments have been made: cultivations of staphylococcus have been inoculated upon the cutis and have led to the formation of small abscesses. Similar cultivations have been rubbed into the normal skin of the arm, and have induced the formation of numerous impetigo pustules, of boils, and, in one case, of a large carbuncle having more than twenty openings through which sloughs came away. Lastly, these organisms have been injected into the subcutaneous tissue and abscesses resulted.

MODES OF SPREAD OF AN INFLAMMATION.—As has been before remarked, spread of an inflammation implies the spread of its cause before it. Now, it is difficult to imagine any conditions under which a mechanical or a physical irritant can advance, under natural conditions, from the spot at which it first acts upon the body; and although it is conceivable that an irritant chemical due to faulty metabolism on the part of a group of cells might soak from the morbid area into the surrounding tissues and thus excite a more or less progressive inflammation, we certainly know nothing of such a process. An inflammation which is characterized by a tendency to spread will be found, we believe, to be of bacterial origin. Clinically, we find that inflammations spread by continuity of tissue, by the lymphatics, or by the blood-path; the latter mode of advance, if not also the second, necessitating an irritant in a particular state, for neither a gaseous nor a fluid irritant in the blood could cause a patch of inflam-

mation at a distance from the primary focus, but would irritate the tissues generally. Micro-organisms, on the other hand, having settled at a spot, can spread thence by (1) pushing their way along paths of least resistance as they grow, by being carried for short distances by lymph-streams or by leucocytes which have taken them up, spread of the inflammation by "continuity of tissue" resulting in each case; or (2) they may be carried from the primary focus long distances by the lymph-stream, usually being arrested in the first lymphatic gland they come to, and often exciting a secondary inflammation there, without, as a rule, causing any trace of inflammation between the primary focus and the gland, the bacteria passing through the lymphatic vessels, but being arrested in the sinuous channels of the gland, precisely like the particles of pigment which may be found upon sectionizing a gland above any extravasation of blood; or (3) the bacteria may enter the blood-vessels and be carried about by the blood-stream until arrested, when, under favorable conditions, they will multiply and give rise to a secondary or metastatic inflammation, such as we get in pyæmia in almost all organs or parts, in mumps when the testis or ovary becomes inflamed; and perhaps the albuminuria which arises in diphtheria and scarlatina and other infective fevers owns a similar pathology.

MODE OF ARREST OF AN INFLAMMATION.—The dying out of an inflammation excited by one of the simple causes is easily understood: the causes having been removed, the cells of the damaged tissues begin to exert their inherent tendency to recover from injury, of which we obtain an evidence in the recovery of paralyzed pigment-cells and the resolution of stasis in the amputated leg of a frog. Dead cells and dying are removed by leucocytes, and their places are taken either by new cells springing from the normal tissue-elements or by leucocytes which ultimately develop into scar-tissue. But when once a brood of bacteria has gained a foothold in the tissues and has begun to multiply and spread, the inflammatory process spreading *pari passu*, it is difficult to see how the advance is checked. Clinically, we see inflammations spread rapidly and widely, and yet, perhaps after causing gangrene of a large part of the body, they are ultimately arrested. The fact is, that all the time there is a struggle for existence going on between the cells of the body and the invading parasites, and the victory may lie with either, and may be won perhaps easily, perhaps only after a struggle of which the issue was for

long doubtful. The first effect of an injury is to cause dilatation of the vessels of a part; and Landerer surmises that this flushing of the part is often successful in sweeping away for destruction or elimination from the system bacteria which have settled and begun to exercise their noxious influence. If this does not happen, the germs will probably find their way into the tissues and the inflammation will spread more or less. In the case of pyogenic cocci giving rise to an abscess we have seen (p. 263) that at first a zone of coagulation-necrosis forms round the microbes; that this is infiltrated by leucocytes from outside and by cocci from within; that it softens and disappears, leaving leucocytes and cocci more or less mixed up; but that by the eighth or ninth day sections of the abscess-wall no longer show this mingling of the opposing forces, the leucocytes now forming a compact wall round the central fluid (pus), which contains both dead leucocytes and the cocci. Similarly, beyond the edge of an advancing erysipelas and other spreading inflammations we find a cloud of these leucocytes, no doubt exercising a corresponding function. As to the weapons with which the war is waged, we do not know anything very exact. It may be that the products of the two classes of cells floating in the same nutrient fluid are mutually injurious, and that those of the body-cells tend to render this fluid unfit for the growth of the bacteria. Again, it may be that the bacteria, as is usual with living things, secrete or excrete products hostile to their own existence, and that these at last accumulate in such quantities as to check the growth of the organism. But there is another way in which microbes appear to be destroyed, about which we seem to know something positive. It has long been known that micro-organisms, like other particles, are taken up by leucocytes; attention was first drawn to it by Koch in his account of mouse-septicæmia. In his paper on the "Etiology of Tuberculosis" Koch advances the view that as the tubercle bacilli are incapable of locomotion, the commencement of a tubercle is due to the escape from a vessel of a leucocyte which has taken up from the blood one or more tubercle bacilli. He expresses his belief, founded upon numerous observations of microscopic specimens, that this leucocyte soon sickens, and swells up first into an "epithelioid" cell, then into a giant-cell, and that the bacilli are short-lived, not uncommonly dying and disappearing from a cell, but often maintaining their position there by the production of fresh bacilli—more rarely of spores. Lastly, Metschnikoff[1] has confirmed Koch's observation by a very direct

[1] *Virchow's Archiv*, Bd. xcvi., xcvii.

method. He found that a little crustacean, the water-flea (Daphnia pulex), suitable for microscopic observation, was subject to invasion by a fungus, the pointed spores of which penetrate its intestine and enter its tissues, where they are at once surrounded by amœboid corpuscles like leucocytes. The spore swells, and ultimately breaks into fragments, whilst the victorious leucocytes blend to form a giant-cell. All this goes a long way toward proving that under favorable circumstances leucocytes may take into their substance and destroy these vegetable parasites; and it seems likely that the beneficial effect of moist warmth in inflammation is due largely to the fact that it increases migration and strengthens the army of leucocytes upon which so much depends.

It must not be supposed that giant-cells are always due to the irritation of organisms: they are formed about a purely mechanical irritant, as Baumgarten showed by sticking fine hairs into the cornea of a rabbit, with the result that a typical "tubercle"—giant-cells, epithelioid cells, and leucocytes—formed round about them.

CHAPTER XXX.

FEVER.

DEFINITION.—The term "fever" is ordinarily understood to mean elevation of the body-temperature above the normal, due to increased combustion of tissues. According to this, a person abnormally hot from diminished loss of heat would not be febrile; but elevation of temperature from great muscular effort would be properly described as febrile.

TEMPERATURE IN HEALTH.—The normal temperature of the surface of the body is always lower than that of internal parts, is lower in proportion as we pass from the trunk toward the periphery, and is liable to much greater variations in consequence of change in external conditions. But neither in internal nor in external parts is the temperature constant: it varies in all parts in a tolerably regular diurnal cycle, the minimum and maximum points for the axilla being lower (.5°–2.5° F.) than those for the mouth, and these again are lower (1.5° F.) than the corresponding points for the rectum. The

extremes of normal temperature may perhaps be stated at about 97.5° and 99.5° F., the axilla of an adult in health rarely giving the higher temperature. As a rule, the temperature rises during the day, reaching its maximum between five and eight P. M., and falls during the night to its minimum, between two and six A. M. Slight departures from this rule are frequent. The average temperature of an infant or young person is slightly higher than that of an adult, and there is a further slight fall toward old age; and it is to be noted that the thermotaxic mechanism is not well developed in the young, the temperature of children being easily raised or depressed to an abnormal extent; even an attack of crying may cause a distinct rise. In old age, on the other hand, oxidative processes are feeble and the temperature is much more easily depressed than raised. The diurnal variation occurs typically in people confined to bed and deprived of food. The effect of food is to excite increased metabolism in the large mass of gland-tissue connected with the alimentary tract and to cause a slight rise of temperature: the taking of food, therefore, may quicken a rise or retard a fall. The effect of ordinary exercise is slight, but tends toward a rise: severe exercise, such as prolonged running, produces ordinarily a rise of 1°–2° F., whilst a temperature of 104° is said to have been thus produced. Mental exertion tends in a similar direction, and it is evident that the activity of all protoplasm must do so. The greater activity of all tissues and the combustion of ingesta are the most obvious reasons for the higher temperature during the day; whilst the fact that the temperature during the night is lower than that at rest during the day seems due to the cessation of tissue-activities not necessary to life, to fasting, and to the more active building up of tissue-compounds which causes heat to disappear. It is said that in people who are in active work during the night and asleep during the day the normal course of temperature is inverted.

The Sources of Heat.—Practically, decomposition of the food is the source of bodily heat, and this is effected by the activity of living tissues. Fats, carbohydrates, and hydrocarbons leave the body as H_2O and CO_2, albumen goes out chiefly as urea; whilst, therefore, the whole heat-value of the former compounds is available to the body, the heat-value of urea has to be subtracted from that of the albumen ingested.

The food is the source also of the kinetic energy of muscular organs, and much of this is transformed into heat. Thus, practically, the

whole of the energy of the heart appears as heat, and a good deal of that of the muscles also, owing to friction of parts.

The more active the metabolism of a tissue, the more heat does it produce. Muscle, which constitutes about half the mass of the body, is credited with producing four-fifths of its heat; for even at rest the rate of oxidation in muscle is higher than in any other tissue (see effect of curare-poisoning on temperature, p. 288), and it is greatly increased by exercise. Next to muscle in heat-producing capacity come the great glands, but their function is to a large extent interfered with by fever. It seems, therefore, that in fever the muscles produce even more than four-fifths of the total body-heat: both in health and disease they may well be called the chief "furnaces" of the body. The superficial and peripheral parts of the body lose much more heat by radiation and conduction than they can produce, whilst the opposite is the case with the internal and central parts: these give up their heat to the blood, which distributes it as it passes through the various parts. It follows that the swifter the circulation, the more nearly equal will be the temperature of the superficial and deep parts, the temperature of the former rising and of the latter falling as the rate of flow increases.

Thermogenesis.—It is evident, from what we have said, that muscles have two functions—the performance of work (**motor**) and the production of heat (**thermogenetic**). Each of these implies the decomposition of some body or bodies contained in the muscle; and, indeed, for practical purposes a muscle may be regarded as consisting of these bodies. We know that muscle, even at rest, absorbs O and gives off CO_2 more rapidly than any other tissue, and that the exchange is greatly increased by contraction. The nature of the decomposition effected by the oxidation, and even the natures of the bodies split up, are unknown: it is possible, as MacAlister[1] suggests, that a different substance is decomposed in each of the two processes—thermogenesis and contraction. At all events, these two functions are to a certain extent distinct from each other, the thermogenic function being exhausted by fatigue or by cold long before power of contraction is done away with. Of course the substances decomposed are built up again during rest. Both functions appear to be under the control of the nervous system. Stimulation of a muscular nerve causes dilatation of its vessels and temporary contraction of a muscle and increased production of heat. On the other hand, poisoning by

[1] Gulstonian Lectures, *Brit. Med. Journ.*, vol. i., 1887.

curare—which acts on the nerve-endings in muscle—paralyzes the muscles not only in their motor, but also in their thermogenic, function: an animal capable of maintaining a fairly uniform temperature (*homoiothermic*) thus poisoned becomes incapable of maintaining its temperature, which accordingly varies with that of the surrounding medium (*poikilothermic*), although the circulation is unimpaired and respiration at the normal rate is kept up. This, as MacAlister points out, demonstrates not only that the thermogenic function of muscle depends upon nerves, but also that the share which the muscles take in the production of the body-heat is so great that when they are eliminated only a mere fraction of the body-heat remains.

As the thermogenic function depends so entirely upon nerve-influence, and as the development of heat is always going on quietly in muscle, with frequent rises when the muscle does work, it is plain that a constant stream of nerve-influence must be transmitted to the muscle. MacAlister believes that a constant thermogenic tone is maintained in resting muscle—probably is the result of the action of two opposing centres, one of which is thermogenic and sends out impulses (destructive or *catabolic*) exciting to the decomposition of the thermogenic substance and to the development of heat, whilst the other inhibits the destruction of tissue more or less, and permits or excites it to repair its substance, its impulses being therefore spoken of as *anabolic*. This theory is constructed upon what we know of the heart-innervation, the sympathetic being the catabolic nerve, the vagus the anabolic.

The thermogenic (catabolic) fibres seem to run with, if they are not identical with, the motor-fibres, and, as we have seen, they are similarly affected by curare. Aronsohn and Sachs have shown that stimulation of a small area inside the posterior end of the corpus striatum causes rapid rise of the rectal temperature, which reaches its height in twenty-four to seventy hours: this is accompanied by increased absorption of O and discharge of CO_2, and the urea-discharge rises 25 per cent. By constant gentle stimulation this truly febrile state may be maintained for hours, no muscular contraction being excited by interference with the motor tract, nor any vaso-motor change. This seems to show that a tract of thermogenic fibres runs down inside the tail of the caudate nucleus.

With regard to anabolic fibre, Eulenburg and Landois discovered in the motor region of the cortex of a dog's brain two areas, the destruction of which cause marked rise of temperature (2.7° to even

23.4° F.) of the opposite arm and leg. Irritation of these centres causes cooling of the limbs on the opposite side. It would appear, therefore, that we have here to deal with a centre in constant action restraining thermogenesis on the opposite side of the body: the temperature rises when the influence of the centre is removed. The effect is greater and more general when both centres are destroyed. The fibres from this centre seem to pass down close to the great ganglia, through the crura cerebri and pons, to the medulla, in or below which they cross to the opposite side. Section between the pons and medulla causes a similar rise of temperature, the inhibitory influence of these descending fibres being cut off from the tissues; but lower than this a section injures or destroys the vaso-motor centre, and the loss of heat is now so great that the temperature falls and tissue-metabolism is much diminished by the cooling of the body. Even when wrapped in wool it is only in robust animals that a rise of temperature occurs from removal of the inhibitory influence of the thermal cortical centres when the vaso-constrictor fibres are also paralyzed (Wood).

These thermal inhibitory centres act upon thermogenic centres in the cord, and seem to be kept constantly excited by stimuli through sensory nerves from the periphery. Heidenhain has shown that stimulation of a sensory nerve causes a fall of temperature of the whole body. It is well known that a concomitant effect is rise of arterial tonus everywhere except in the area of the stimulated nerve: the circulation would therefore be quickened and loss of heat from the skin increased. Stimulation of a sensory nerve thus tends in two ways to reduce temperature. As the vaso-motor centre lies in the medulla, and the thermal inhibitory centres are apparently in the cortex, after section just between the medulla and pons stimulation of a sensory nerve should raise the blood-pressure, but not lower the temperature; and this Wood found was always the result.

Ott, in the *Journal of Physiology* (August, 1887), warmly advocates the view that fever is mainly a disease of the nervous system, the thermogenic centres being stimulated by various substances thrown into the circulation—the proof of this, according to Ott, lying in the fact that curarization prevents the development of fever under circumstances which would otherwise certainly give rise to it. In the *Therapeutic Gazette* (U. S.), Sept. 15, 1887, Ott states, in opposition to Eulenburg and Landois (see above), that injury of the cortex over the basal ganglia has little effect on the temperature, but lesions

of the cortex below the thalami cause a slight transient rise. Ott speaks of four heat-centres: 1. A transverse section of both corpora striata caused a rapid rise to 111.5° F.; a section one millimeter in front of the striated body has a similar effect, but sections farther forward do not disturb the temperature. Lesions below the striate body cause fever. 2. The spot internal to the caudate nucleus, described by Aronsohn and Sachs, is spoken of as a "centre." 3. Transverse section of the anterior and inner end of the optic thalamus causes a rapid rise of temperature, followed by an almost equally rapid fall, the normal being reached in ten to sixteen hours. 4. Lastly, a puncture between the striate body and the anterior end of the optic thalamus causes a rapid rise of temperature, with a slow descent to normal on the third or fourth day. The highest temperatures seem to follow injury of the optic thalamus, but the fever endures longest after injury of the centres numbered 2 and 4. Ott regards these centres as either inhibitory or excitor, according to the nature of the impulses sent to them from the peripheral nerve-endings.

Such being a short statement of the little that is known of the nervous mechanisms concerned in thermogenesis, we must now pass on to consider the control of temperature (**thermotaxis**)—*i. e.* the manner in which **thermogenesis** or heat-production and **thermolysis** or heat-loss are so exquisitely balanced that the body-temperature remains practically constant under widely different conditions.

Thermotaxis.—It is obvious that the temperature of the body is the expression of the balance, so to speak, between heat-production and heat-loss, and may be regulated by acting upon one or other factor. The temperature is no guide as to the actual amount of heat produced or lost in any given time.

That variation in **heat-production** does aid in regulating the temperature appears from the fact that external cold increases the absorption of O and the CO_2 discharge, whilst external heat diminishes both. Stimuli from the periphery reaching the thermal centres along sensory nerves no doubt lead to efferent impulses—from the centres to the tissues—which regulate thermogenesis. After what has been said above it will be accepted that the central nervous system can powerfully influence thermogenesis, if it does not absolutely control it, although we are still very uncertain as to the position and nature of the heat-centres and as to the course of the fibres connected with them.

But the temperature is apparently far more readily controlled by acting upon the **heat-loss.** Thus we find that heat causes dilatation

of the cutaneous vessels, sweat appears upon the surface, and the skin from being moistened and filled with fluid becomes a better conductor. Consequently, loss of heat by radiation, conduction, and evaporation—the three chief ways in which heat is lost to the body—is much increased. Under the influence of cold the skin is pale, shrunken, and dry, and loss of heat from it is reduced to a minimum. Next, rise of temperature causes a rise, and diminished temperature a fall, in the heart-beats: the heat-loss will vary directly as the volume of blood passing through the skin in a given time is greater or less. Rise of temperature increases also the number of respirations, and this leads to the warming of a larger volume of air almost to the body-temperature, and to the evaporation of a larger quantity of water: depression of temperature acts in an opposite manner.

THE SYMPTOMS OF FEVER.—The essential symptom is rise of temperature above the normal, due to increased thermogenesis, *sometimes* aided by diminished thermolysis.

Thermogenesis is probably always increased, whatever the stage of the fever. It is due to increased tissue-metabolism, as is shown by the facts that more O is absorbed, 60–70 per cent. more CO_2 is given off, 30–60 per cent. more urea leaves the body, the uric acid discharge is increased, the potash eliminated in the urine may be seven times the normal amount, and the urinary pigment (derived from hæmoglobin) may be increased twenty-fold. Of course the higher degrees of tissue-destruction correspond to the more severe degrees of fever.

In speaking of increased thermogenesis in fever we mean that a febrile patient will produce more heat in a given time than a healthy person *upon the same diet* and *under similar circumstances;* not necessarily more than a healthy person on ordinary diet, though even this may be the case. The balance of heat in favor of the febrile patient is of course due to the *excessive* combustion of his tissues.

Thermolysis is usually increased, loss of heat being excessive both by skin and lungs. In the early stage of many fevers of acute onset, however, the capillaries of the skin are strongly contracted, and the skin is consequently more or less pale, shrunken, and cool. With this state of matters loss of heat is markedly diminished. Heat-production is increased at this stage, and the internal temperature is found to be several degrees above that of the surface. Under these circumstances the sensory nerves of the skin naturally convey to the

brain the impression of cold, and the patient suffers from **chills** or from actual **rigors** or violent shivering attacks, the muscular movements of which must give rise to increased development of heat. As the "cold stage" passes off the skin becomes reddish, hot and burning to the touch ("hot stage"): dissipation of heat is markedly increased, but in spite of this the body-temperature continues to rise. Finally, sweat appears ("sweating stage") upon the surface; the skin remains vascular, is moist and full of fluid, and is therefore a better conductor of heat. The loss of heat now reaches its greatest height, the loss due to radiation and conduction being great, and to this is added free evaporation. During the cold and hot stages thermogenesis is much increased, but during the third it may be excessive, normal, or subnormal. Frequently these stages are not present even in fevers of acute onset and course, but they are all seen typically in a "fit of ague" or in an ordinary "rigor."

As a *consequence* of the rise of temperature (external heat has a similar effect) the heart beats more quickly, the volume of blood passing through the skin in a given time is increased, and more heat is thus given off. No exact ratio can be stated by which the rise of **pulse** per degree of rise of temperature can be calculated: much depends upon the individual, especially whether child or adult, and a good deal upon the cause of the fever—*e. g.* scarlatina raises the pulse much more than typhoid.

Respiration also is quickened—in children more than in adults—and thus more heat is lost by warming the inspired air and volatilizing the water with which it returns charged.

Thermotaxis.—The heat-regulating mechanism is disturbed and fails to maintain the balance between heat-production and heat-loss. Were this balance maintained as in health we should have a stable temperature at a higher level than the normal. But the chief characteristic of the temperature in fever is its instability: cold, food, excitement, effort, antipyretic drugs, all affect it much more markedly than the temperature in health. As MacAlister says, the tolerably regular daily fluctuation of the temperature in fever (evening rise and morning fall) shows merely that *all* the thermal processes are not utterly disturbed, some which are rhythmic in health remaining so in disease.

Symptoms due to Degeneration of Tissues.—The effect of an abnormally high temperature upon protoplasm is to damage it and ultimately to induce cloudy swelling, which is the first stage of fatty degeneration (p. 77); poisons circulating in the blood have very likely

a share in producing this result. The first result as regards the **nervous system** is often headache, inability to think or to apply one's self, general sluggishness of mind, loss of self-control, hyperæsthesia of special senses; then comes delirium, at first at night and for periods only, but often becoming more marked and constant. Vague muscular pains are common in early stages: even in their absence unwillingness for exertion is marked; the muscles waste markedly and their movements become weak and tremulous. The nervous system has a large share in tremor, and is responsible for such a symptom as constant picking at the bed-clothes. The **heart,** among other muscles, fails progressively in quality and power, and as it does so its beat becomes more frequent and less effective. Here, again, it is probable that the nervous system is partly at fault, its inhibitory influence through the vagus upon the heart being impaired and ultimately lost. Similarly, **arterial tone** is progressively lost. The result of the progressive failure of the heart-force and arterial tone is that the **pulse,** which in a healthy individual at the commencement of a long fever is quick, full, and strong, often inclined to hardness from high arterial tension, becomes as the fever progresses quicker (without any further rise of temperature), softer, and fuller, the fulness and softness being due to loss of arterial tone, whilst the heart-beat is still strong; the softness increases as the arterial tone yields further, but the size diminishes as the still more rapidly beating heart fails to fill the vessels: ultimately, the pulse is very small, soft, and frequent ("thready"). A rising pulse against a steady or falling temperature is therefore regarded as *the* sign of a failing heart.

Digestion is much disturbed and appetite for solids is usually lost (**anorexia**) in all acute fevers. **Secretion** of the glands along the alimentary tract is more or less impaired. There is usually a tendency to **constipation,** due probably to sluggishness of the intestinal muscle, to lack of fluid, and perhaps to absence of some of the normal stimuli to contraction. **Excretion,** as tested by the appearance of a salt in the urine, is said to be slow in fever. The **urine** is small in quantity, high-colored, yields copious precipitates of urates, and holds urea, uric acid, and potash in excess (p. 292). With the excess of coloring matter in the urine may be taken the fact that in fever there is progressive decrease of red corpuscles in the blood, but increase of leucocytes.

The **temperature in fever** varies greatly, and the terms slight, moderate, and high or severe are used respectively to indicate fevers

in which the temperature lies between (roughly) 99.50°–101°, 100°–103°, 102°–106° F. Above 106° F. the fever is called **hyperpyrexia**, and a temperature above this point enduring for any length of time is usually fraught with the greatest danger to life. Failing to produce death, a high temperature leads to early and widespread fatty degeneration. When the temperature of the body as a whole reaches 109°–110° F. death occurs, as in sunstroke, apparently from a decomposition of the tissues. So-called "**paradoxical temperatures,**" even up to 128° F.,[1] have been recorded as occurring in hysterical individuals: often there has been much reason to fear deceit, but it must be admitted that the most careful watching has failed to detect it. In some cases very high temperatures have recurred again and again during a considerable period of time; they are often quite local, the temperature of the corresponding part on the opposite side, for example, being normal or almost normal, and they are accompanied by few or no symptoms. Wasting especially is absent. Hale White[2] regards these cases as of central origin, due to perverted action of the caloric centres, which he supposes to be like that of the motor area in hysterical hemiplegia.

Febrile temperatures almost always exhibit a tendency to rhythmic daily variation like the normal temperature, being higher in the evening than in the morning. Sometimes the opposite is the case, however, and the temperature is then said to be of the *inverted type.* When the daily variation does not amount to much more than that found in health (about 2° F.), the fever is termed "*continued.*" When the variation is greater than this the fever is "*remittent*"—*hectic* fever, which accompanies chronic suppuration, affording the best example. When the fall between two maximum points reaches to or below normal, so that there is a fever-free period, the fever is said to be "*intermittent.*" Of this variety "intermittent fever" or ague is the type, its attacks coming on regularly, at a certain hour, every day (*quotidian*), every other (*tertian*) day, or occasionally every third (*quartan*) day. This periodicity is certainly due to corresponding periodicity in the activity of the cause of ague, which, with almost equal certainty, may be said to be some micro-organism.

In all febrile attacks we have certain stages: (1) The **onset** or rise of temperature; (2) the **acme** or height of the fever; and (3) the **fall** of temperature and ending of the fever. The **onset** may be sudden, the temperature rushing up to its full height in twenty-

[1] Mahomed, *Lancet*, 1881, vol. ii. p. 190. [2] *Guy's Hosp. Rep.*, 1884, p. 65.

four to thirty-six hours, or gradual, rising from day to day till the acme is reached, and this with such constancy in certain diseases as to be more or less diagnostic of them. The sudden onset is frequently accompanied by that contraction of the skin-vessels and diminished loss of heat by this path which induces sensation of cold and shivering (**rigor**), although the internal temperature is markedly raised. In children, in whom the controlling power of the nervous system is less developed than in adults, a convulsion usually replaces the rigor. The **fall** of temperature, too, may be sudden (**crisis**), and accompanied by "critical" sweating or diarrhœa; and sometimes the fall sinks far below the normal (**collapse temperature**), and the patient is in great danger of dying, or actually dies, collapsed. On the other hand, the fall may be gradual (**lysis**). These two modes of ending also are characteristic of certain diseases. Such peculiarities are doubtless dependent upon as yet unknown peculiarities connected with the growth and death of the ferments, which appear to be the causes of most fevers running a "typical" course.

POST-MORTEM RISE OF TEMPERATURE.—There is reason to believe that in many, if not all cases, a slight rise of temperature occurs after death: it is more marked in those dying suddenly or of acute diseases than in those who perish from chronic exhaustion. It is most marked in cases of fever due to the presence of a ferment in the blood or to some mechanical irritant of the thermal centres or paths, and in which death occurs with a high and rising temperature. Tetanus is probably the best example. The explanation is, obviously, that death of the body (**somatic death**), as a whole, is not accompanied by extinction of function in the tissues; in these thermogenic processes continue for a longer or a shorter time; the energy of the destructive metabolism varies (1) according as the tissues are exhausted or contain a plentiful supply of the thermogenic substance, and (2) according as the stimulus to the decomposition is of normal or of pathological strength. Whilst, then, the production of heat continues, loss is greatly limited by cessation of the circulation.

ETIOLOGY OF FEVER.—The foregoing account has shown that the essential condition in fever is increased thermogenesis due to increased breaking down of the tissues, and especially of the muscles. It is possible that some decomposition of the food absorbed goes on in the blood, but catabolism takes place almost entirely

the tissues, not in the internal medium for the distribution of food and heat. Various other views have been held; for example, that in inflammatory fevers the blood was heated to the fever temperature in its passage through the inflamed part, which was regarded as a heat manufactory (see p. 257), or that the fever was due to energetic contraction of the skin-vessels, which greatly diminished loss, whilst production remained unaffected, and heat consequently accumulated in the system (Traube). But such a contraction of vessels is by no means constant, and when it occurs is not of long persistence; a high temperature and a freely sweating skin commonly occur together; and lastly, calorimetric observations have demonstrated the increased thermogenesis; and, if support were required for the view that fever is due to increased destruction of tissue, it is found in the observations on the urea and CO_2 discharge.

We have further seen reason to believe that thermogenesis is under the control of a cerebral centre or centres, which, again, probably control thermal centres in the cord; but in the present state of knowledge it is impossible to speak certainly of the position of these centres, of their function (excitor and inhibitory), or of the paths of their afferent and efferent fibres. The effect of curarizing an animal (p. 289) would seem to demonstrate that, normally, heat-production in muscle, like contraction, takes place only in response to a stimulus along a thermal (catabolic) nerve; but it does not prove the impossibility of *directly* stimulating the muscle to produce heat, especially as we know it can contract after its motor nerve is dead. It is evident, therefore, that causes of fever may act upon the tissues *directly* or *indirectly through the nervous system* in inducing the increased thermogenesis. In certain cases—*e. g.* nervous or hysterical fever—it seems impossible that the cause can act upon the tissues otherwise than through the nervous system; but in the majority of cases it may act either way, and until recently it has generally been assumed that the action has been direct from the blood upon the tissues.

Like inflammations, fevers may be divided into the **infective** and **non-infective.** The **infective fevers** are of course such as are due to the multiplication in the body of a micro-parasite. This explanation serves for the group of "acute specific fevers," malaria and febrile diseases, in which there is no inflammation present, at least in the early part of their course. These constituted the old groups of **primary** or **essential fevers.** In some (typhus, malaria) there is no inflammation; but in many an inflammation appears (of throat, nose,

and eyes, skin, intestine) too late and often too slight to account for the fever present. It answers also in cases of fever **secondary** to a wound through which organisms have entered the body to multiply in it—*e. g.* septic infection and pyæmia (*q. v.*), erysipelas, lymphangitis; and the large group of fevers secondary to inflammations (**inflammatory** fevers), practically all of which are infective, must be included under the heading. In most of these "secondary" fevers the pyrogenous materials are manufactured by organisms in **the body,** but localized, and are cast into the blood.

In the **non-infective group** we find, first of all, two wound diseases—septic traumatic fever or simple wound fever, and its more intense form, acute septic poisoning or sapræmia. Here the poison is manufactured (as is believed) by septic organisms in the wound—**outside** the body, whence they are absorbed. Next we find **simple traumatic fever,** which ensues upon "simple" injuries (contusions and fractures). It is generally slight, and the most probable explanation of it is the absorption of fibrin-ferment (and very likely other pyrogenous bodies) from the seat of injury; possibly, too, irritation of nerves, by the injury, fragments of bone or tissue, may have some effect in causing the fever, but *strong* irritation of a sensory nerve (p. 290) causes depression of temperature. **Aseptic traumatic fever** which occurs in aseptic wounds is probably due to the same causes as the simple traumatic. **Nervous (hysterical) fever** is supposed to be due to removal of inhibitory influence of higher over lower thermal centres, or perhaps to direct excitation of the lower thermogenic centres. It is not very uncommon to meet with irregular temperatures, not accounted for by any wound or recognizable disease, in women, and less commonly men, who are the subjects of hysterial phenomena. It is in such that "paradoxical" temperatures (p. 295) have been noted. Again the rise of temperature which occurs in children, puerperal women, and other weakly adults from various emotions and other slight causes—*e. g.* the rise which is so commonly found after an entertainment has been held in a ward—seems to be an example of nervous fever.

Then cases of nervous injury or disease not uncommonly occur in which one cannot help suspecting that thermo-inhibitory centres or fibres are destroyed or that thermogenic centres or fibres are irritated. Hale White[1] has brought a number of such cases together. In a most interesting case of bullet-wound of the head accompanied by fever,

[1] *Loc. cit.*

not otherwise explained, it was found that the motor area of the cortex, corresponding to Eulenberg and Landois' heat-centre in the dog, had been destroyed. The inhibitory influence of this centre may apparently be cut off or destroyed by sudden and extensive intracranial hemorrhage, by hemorrhages, scleroses, and tumors of the brain, so placed as to destroy inhibitory fibres or to irritate thermogenic tracts. It has long been known that injuries and tumors of the cervical cord, along which most thermal fibres must pass, are apt to cause marked fever. In a girl with a fracture of the cervical spine Teale recorded a temperature of 120° F., recovery ultimately occurring: some regard this as an instance of hysterical fever.

Lastly, there are many fevers of which we are quite ignorant of the pathology—*e. g.* the fever met with in various anæmic states, in lymphadenoma, and occasional cases of malignant disease.

CHAPTER XXXI.

THE INFECTIVE GRANULOMATA.

THE infective granulomata, which include tubercle, lupus, syphilis, glanders and farcy, leprosy, actinomycosis, and rhino-scleroma, have many analogies with tumors. They all consist of cells, varying between lymphoid and giant-cells in size, lying in a scanty matrix, and the collection of cells presents to the naked eye a more or less defined outline. The lesions therefore resemble sarcomata in structure. Many of them develop without any obvious cause, and are accompanied by no signs of inflammation: they often persist for long periods, rarely undergoing absorption (except gumma, especially under treatment) or development into a permanent tissue, but often degenerating early; and, lastly, most lesions of this kind have an *infective* power, disseminating poison by both blood and lymphatic vessels. In all these respects the above-mentioned new formations resemble malignant tumors, but they differ from them etiologically. In the case of some we know—and there is good reason in all for believing—that the tumor-like nodules are products of chronic inflammation excited by the growth of organisms at certain points in the tissues. Irritation is maintained so long as the fungi grow, and therefore the processes are often chronic. Vascularization is imper-

fect or absent, so degeneration is the rule. Infection of other parts is due to spread of the organism, not of the new cells, from the primary focus.

The above diseases are as specific as the "acute specifics." Their essential lesions necessarily have a decided resemblance; but the primary seats, modes of generalization, modes and times of degeneration, and the clinical symptoms establish the most distinct diseases. The transmissibility from person to person of syphilis and glanders is well known; experimentally tubercle can be transmitted, and the clinical evidence of its communicability from man to man is too strong to admit of doubt. Leprosy has been acquired through a post-mortem wound, and experimental inoculation has been successfully performed upon a criminal. Actinomycosis has been transmitted from man to animals. The name adopted for the group originated with Virchow and is used by Ziegler. It seems better than any other to express the nature of the lesions—tumor-like bodies consisting of granulation-tissue and locally or generally infective.

Tubercle and Tuberculosis.

By "tuberculosis" is understood an infective disease which is characterized anatomically by the formation of those small nodular lesions known as **tubercles.** The distribution of these lesions may be more or less general—**acute general tuberculosis**; or they may be limited to small areas—*e. g.* synovial membrane of a joint or a pleura—**local tuberculosis.** The latter, as a rule, runs a much more chromic course than the former, and perhaps its chief danger is that it may serve as a focus for general infection.

The virus of tubercle does not always produce nodules. Laennec divided tubercular lesions into the **nodular** and the **infiltrating.** In the latter case a diffuse inflammation is found, and microscopic examination shows the presence of numerous non-vascular collections of cells, not aggregated into visible nodules, but separated by an ordinary round-celled infiltration. The presence of the ordinary tubercles in a tissue always excites more or less inflammation, as is best seen in serous membranes.

NAKED-EYE APPEARANCES.—Tubercles are divided into **gray** and **yellow**, the latter being later stages of the former. **Gray** or **miliary** tubercles (**gray granulations**) are grayish, semi-translu-

cent, rounded bodies, varying from just-visible points to nodules the size of a pin's head, or sometimes larger, firm and shot-like, distinctly circumscribed in appearance, and projecting from the surface of section. **Yellow** tubercles are generally larger, sometimes forming masses the size of a cherry or small walnut, and softer than the gray. In some cases most of the tubercles present are gray, whilst in others all are yellow; but it is frequently possible to trace every stage in the formation of a yellow from a gray nodule. Fatty degeneration, commencing centrally, is the main cause of the difference between them. The larger masses of yellow tubercle are formed, not by growth of individual tubercles, but by the blending of several tubercles which lie close together. It is often possible to recognize a narrow gelatinous zone, which consists of undegenerate tubercles round the cheesy mass, and tubercles may be seen radiating from the cheesy focus into the surrounding tissues, indicating that infection from the central mass leads to the formation of fresh tubercles in its immediate neighborhood, and these, as they enlarge and degenerate, fall into the central mass. A yellow mass thus formed is called **conglomerate tubercle.**

SEATS.—The skin and subcutaneous tissue, the mucous membranes—respiratory, alimentary, and genito-urinary—and the serous and synovial membranes are very commonly affected; so also is the

FIG. 89.

A Multinucleated Cell from the Lung in a Case of Chronic Phthisis, showing the large number of nuclei with bright nucleoli. × 400.

pia mater. The dura mater, the ependyma, and the endocardium rarely suffer. Of the organs, tubercles are frequent in the lymphatic

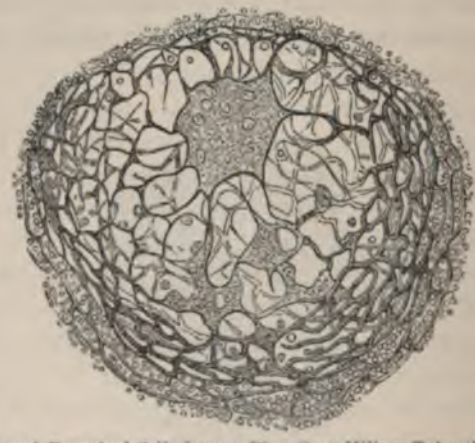
glands, lungs, liver, spleen, kidneys, and testes; less common in brain and spinal cord, adrenals, and prostate; rare in the heart,

FIG. 90.

A Multinucleated Cell from the Lung in a Case of Chronic Phthisis, showing the branched processes, which are continuous with the reticulum of the surrounding indu growth. Some of the processes are in connection with smaller nucleated elements. ×

vary glands, and pancreas; very rare in the mamma, ovaries, thyr and voluntary muscles. They are common in bone, especially can

FIG. 91.



Multinucleated and Branched Cells from a Firm Gray Miliary Tubercle of the Lun Case of Acute Tuberculosis: Wide meshes are seen in the immediate vicinity of the enclosing a few lymphoid elements. The branched processes are directly continuous the reticulum of the tubercle. × 200.

lous. They occur especially in childhood and early adult life, bu age is exempt.

HISTOLOGY.—On examining microscopically even the smallest visible tubercle it is found to be formed by the aggregation of more minute bodies, *each of which*, as a rule, contains the following elements: Centrally, either one or more multinucleated **giant-cells** (Figs. 89 and 90) or some granular débris surrounded by giant-ells; outside the giant-cells are usually, but by no means invariably, seen large cells with big nuclei and granular protoplasm, often called **epithelioid cells**; and outside these, again, there is a zone of **lymphoid** elements which has no definite external or internal limit. The giant-cell or cells in many cases send off processes which anastomose and form an open network (Fig. 91), in which the other cells, especially the epithelioid, lie. The lymphoid cells are commonly contained in the meshes of a homogeneous or more or less fibrillated reticulum, which in some cases, especially in slowly-developed lesions, is well marked (Fig. 92), in others is less prominent, in others, again, is entirely wanting.

FIG. 92.

Portion of a Gray Miliary Tubercle of the Lung, showing the reticulated structure often met with in these nodules. × 200.

The above elements are just those which Ziegler found between his glass plates in chronic inflammations (p. 260). There is nothing specific in any one of them—*i. e.* no tubercle-cell, as was formerly supposed—but the larger forms are commoner in tubercle than in other chronic inflammations, perhaps because tubercles are *non-vascular*. In the pia mater, it is true, tubercles are generally found upon one side of or surrounding a small vessel lying within its sheath and often occluding its lumen, and sometimes compressed vessels can be seen lying between the outermost cells. But no new vessels are formed, and those natural to the part, unless they are of some size, are soon occluded by pressure. It will be remembered that the development of giant-cells in inflammatory exudations occurred inversely as the development of vessels, and that imperfect vascularization led to those degenerative processes which are so characteristic of tubercle. Miliary tubercles are so small that they might well be nourished for a time by surrounding vessels; and one cannot help feeling that this might continue and caseation be indefinitely postponed were it not for the action of the bacilli.

A non-vascular nodule of the above structure is the anatomical characteristic of tubercle, but it is not microscopically distinguishable from the products of other very local chronic inflammations.

We have already (p. 286) noted that Baumgarten produced typical "tubercles" in a rabbit's cornea by sticking fine hairs into it; Laulanié states that in the lung disease caused by the *Strongylus vasorum* in dogs the ova and embryos may be seen in giant-cells surrounded by zones of epithelioid and lymphoid cells; and in actinomycosis of animals an exactly similar arrangement of cells is found round about the central *actinomyces* or fungus of the disease.

Nor can the above structure be said to be constant. For, especially in acute cases, soon ending fatally, some of the tubercles may consist of small round cells, no epithelioid or giant-cells having developed, and in the lung the alveolar epithelium often enters largely into the constitution of the lesions. Tubercles visible to the naked eye will, however, generally consist of aggregations of nodules of the above structure (Fig. 102).

As to the **sources of the cells** in tubercle, there has been much controversy, some maintaining that they result from hyperplastic processes among connective tissues (endothelium of lymphatics and serous membranes, adventitia of vessels, ordinary connective tissue); others that they are or develop from white corpuscles; and others, again, that epithelium frequently takes a large share in their formation. We regard Ziegler's experiments (p. 260) as showing that leucocytes frequently produce all the cell-forms met with in "tubercles" as above described; also the reticulated fibrous stroma. Koch's observations on the origin of epithelioid and giant-cells (p. 285) are in accordance with this view; and we should therefore, whilst admitting that the fixed connective-tissue cells *may* multiply and take their share in the formation of these nodules, hold that the leucocytes are a proven and far more likely source. When, however, we come to deal with parts in which the third source (epithelium) is present, as in the lung, liver, kidney, or testicle, there can be no question but that the epithelial cells multiply freely. In a lung affected by acute miliary tuberculosis we find that many, even the majority, of the nodules do not possess the lymphoid structure above described, but are collections of epithelial cells in the alveoli, and giant and epithelioid cells may be present, formed apparently from alveolar epithelium, as Klein and Cheyne assert. Koch also regards certain pigment-containing giant-cells as originating in alveolar epithelium, and quotes Cheyne's observations[1] on the presence of giant-cells actually in the alveoli in support of his own.

[1] *Practitioner*, April, 1883, p. 310.

Plausible as this origin appears, such observations hardly *prove* it; we have seen in the general account of inflammation (p. 249) how difficult it is to trace the origin of cells. The conclusion is that a "tubercle" such as is described above originates probably from leucocytes: but if the term may be extended to cover the mass of epithelial cells which results from the catarrhal pneumonia excited by the tubercle bacillus in the alveoli, a "tubercle" may be of epithelial origin. Such a tubercle will have no reticulum and tends to very early caseation. Its resemblance to the typical tubercle lies in its naked-eye appearance and its etiology. Giant and epithelioid cells have been described as arising from the epithelial cells of the liver (Cheyne), kidneys (Julius Arnold), and testes (Gaule).

SECONDARY CHANGES.—Caseation.—Tubercle invariably undergoes more or less fatty metamorphosis, although the extent of this varies considerably, and in some cases the nodules may become developed into an imperfect fibroid structure. The occurrence of retrograde metamorphosis is mainly owing to the non-development of new or obliteration of pre-existing blood-vessels which accompanies the growth of the lesions. The change commences in the centre of the nodule, this being the part first developed, and consequently that which is the farthest removed from vascular supply: it is also the part at which the bacilli are at first most numerous, and it is therefore most exposed to their deadly influence. The nodule breaks down into a granular fatty débris, so that its central portions soon become opaque and yellowish (Fig. 93). In some cases the process of disintegration is rapid, whilst in others it is more gradual. It is usually most marked in the larger and more diffused lesions, and hence it is these lesions which are most commonly of a yellow color and soft consistence ("yellow tubercle").

FIG. 93.

One of the Gray Nodules from the Lung in a Case of Acute Tuberculosis, which is becoming opaque and soft in the centre. (Diagrammatic.)

Fibroid Change.—In other cases the retrograde change is less marked; the central portion, as a rule, undergoes fatty degeneration and is more or less completely absorbed, whilst the ring of leucocytes which intervenes between the bacilli and the healthy tissues is transformed into a dense, contracting, fibrous capsule. Ultimately,

a mere scar alone may remain, but points of fatty degeneration are frequent and may undergo further changes.

It will be noted that this "fibroid change" is simply the encapsulation of a slightly irritant foreign body, and might take place in exactly the same way if a bullet or piece of wire lay in the tissues in place of tubercular organisms in fatty detritus. This more or less complete replacement of the tubercular tissue by scar-tissue occurs in the smaller lesions and in many of larger size which open upon the inner or outer surface of the body, and thus discharge the infective material: it is obviously protective to the organism against generalization from the focus in which it occurs, and indicates that the tissues have gained the upper hand; they have hemmed in the bacilli completely. There is the same antagonism between the organisms and the tissues here as in other diseases; and, fortunately, the resisting power of the latter is often sufficient to enable them in the long run to overcome the invaders—a fact which we were somewhat slow to appreciate. But frequently the predisposition of the tissues to suffer from *B. tuberculosis* is so great or the dose of the organisms is so large—as when most of the contents of a small cavity which has just burst into a bronchus is sucked by inspiration into other air-tubes—that a widespread, diffuse inflammation results; and the more extended the lesion, the more rapidly and freely the inflammatory products caseate.

Sometimes, especially in cases which have run a chronic course and in which the diagnosis may have been "chronic bronchitis," hard, glassy bodies, often specked with black pigment, are found in the lung-tissue. There is no caseation, and the microscope shows the masses to consist of almost hyaline fibrous tissue. This complete fibroid transformation is said by Birch-Hirschfeld occasionally to occur in lymphatic glands. It would appear to us to indicate that the bacilli are dead, whilst when caseation occurs they have probably formed spores, and the fatty débris remains for an unknown period infective.

Calcification frequently ensues upon caseation, when the cheesy products become encapsuled and almost all fluid is absorbed: the deposit of earthy salts in this truly cheese-like material converts it either into a gritty mass or into a more or less irregular stony body. Caseous mesenteric glands are especially prone to this infiltration.

Softening and Chronic Abscess.—Caseous masses frequently do not dry and become encapsuled, but soften and break down into the

pus of a chronic abscess; or, again, having become encapsuled and even calcified, softening occurs round about them and a chronic abscess forms and leads to the discharge of the dead material. It is the smaller encapsuled foci, and especially those which lie deep in the substance of organs, that become dry and calcified, whilst the extensive, diffuse lesions and those lying near a skin or mucous surface tend to soften; in other words, the less the resistance of the tissues to the infective process or the greater their proneness to be irritated by the tubercular organism, the greater is the tendency to softening. It seems likely that it is to this irritation of the tissues that the exudation of fluid into the cheesy mass, which changes the latter into a chronic abscess, is due; for an examination of the "pus" of a chronic abscess shows that it consists chiefly of fatty granules suspended in fluid, with here and there a fattily degenerated, granular leucocyte. The fluid, therefore, is quite different microscopically from that of an acute abscess (p. 95), and it differs also to the naked eye, being generally whiter and thinner, and it often contains curdy masses which may be either gritty or rendered solid by calcification. Being formed by the suspension in an albuminous fluid of fatty particles derived from the fatty degeneration of cells, the "pus" of chronic abscesses has received the name of "pathological milk." The enormous majority of chronic abscesses are of tubercular origin. A tubercle forms, spreads and softens as above described, the originally firm swelling becoming more and more fluctuating as the softening proceeds: so chronic is the process that there is often no sign of inflammation ("cold" abscess) until just before bursting, when the tense skin where it is pointing becomes red, shiny, and thins progressively, and ultimately the epidermis bursts, allowing the cavity to discharge its contents. The wall of such a cavity is lined by a thick layer of pale purplish granulation-tissue, in which are yellow foci as a rule, and it is so loosely adherent to the surrounding tissues that scraping with a sharp spoon easily detaches it and brings it away either entire or in large pieces. The tissues beyond it are not infiltrated. It is very important that the wall should be removed from such abscesses and the base from the ulcers resulting from their bursting; for the granulation-tissue is infected by the tubercle-bacilli, and will continue to caseate and soften in spots, and perhaps slowly to invade surrounding parts; at all events, healing is impossible until the diseased layer has been cast off and healthy granulation-tissue has replaced it.

This account of the formation of a chronic abscess holds good wherever such may appear: in the subcutaneous tissue (**subcutaneous strumous nodule,** so common in children); in a lymphatic gland, the "strumous abscess" *par excellence;* in the lung, where sooner or later it bursts into a bronchus, discharges its contents, and forms a "**cavity**" or "**vomica;**" in the thickened synovial membrane of a scrofulous joint (**white swelling**); or in a bone, as we see in caries of the spine. The chronic abscesses which arise in connection with deep bones, especially those of the spine, are frequently called **gravitation-abscesses,** because the pus often runs long distances among the soft parts before it reaches the surface, and usually in a direction toward the feet. But extension by no means always occurs in this direction, and if it is occurring it is not arrested by placing the patient in the horizontal position; we may therefore conclude that in these, as in all other cases, the pus spreads in the direction of least resistance, and that gravity has little to do with it. Instances have been recorded of abscess starting from the lower dorsal or lumbar spine, entering the sheath of the psoas, causing gradual absorption of its muscular fibres, working its way beneath Poupart's ligament, taking the course of the profunda artery, passing through the abductor magnus into the popliteal space, thence between the superficial and deep posterior leg-muscles, and pointing by the inner malleolus. Such an abscess is contained in a dense fibrous sheath formed by inflammatory thickening of the natural connective tissue, and sometimes strong enough to be dissected out and dried. The cavity is crossed by stoutish bands, many of which contain vessels, so a finger introduced during life must not tear them. The inner surface of the cavity is but slightly vascular—the contrast between the chronic and acute abscess in this respect being very marked—is usually coated with a cheesy deposit of irregular thickness, beneath which lies a very thin layer (as a rule) of granulation-tissue. At the upper extremity is the diseased bone—the *fons et origo malorum.*

In the pus of these abscesses no organisms can be discovered by the means at present in use, yet the pus is infective and produces general tuberculosis when injected into animals. Probably the spores of *B. tuberculosis* are present, but we cannot stain them.

RESULTS.—Recovery may occur after the discharge or complete artificial removal of all tubercular tissue: healthy granulation-tissue then springs up and develops into a scar, filling up and drawing

together the cavity of the abscess or ulcer. There is always loss of substance.

The condition known as **obsolescence,** in which the caseous focus is surrounded by a dense fibrous capsule, often with radiating bands passing from it into the surrounding tissues, as we commonly see at the apices of lungs, is often a practical cure; but, theoretically, it is not one unless the tubercular virus has died or has been destroyed, for so long as it lives it may at any time be carried from the focus into the system at large.

Lastly, **death** frequently results from tubercular processes, both general and local. The acute general tuberculoses, affecting chiefly meninges, lungs, and peritoneum, kill by their general toxic effect, by fever, and by interference with the functions of vital parts—*e. g.* with those of essential cerebral centres by the compression of the effusion. Chronic local tuberculoses kill either by leading to a general outbreak or by exhaustion from fever, pain, and profuse and prolonged discharge, all being most serious when any abscesses or sinuses are septic. Indirectly, a tubercular process may open the door to some infective wound-disease, such as erysipelas or pyæmia.

ETIOLOGY AND GENERAL PATHOLOGY.—In 1857, Buhl, who had noticed the very frequent presence of one or more caseous foci in cases of general tuberculosis, and who had described also the local infection which often occurs round such foci, promulgated the view that a poison capable of giving rise to tuberculosis was generated in the process of caseation of the products of some simple inflammation. Caseation was essential to, and was the cause of, the development of the virus. From the centre of its development the infective material might spread to the neighboring parts or to parts at a distance. Virchow, however, pointed out that caseation occurred in new growths and under circumstances in which all connection with tubercle could be negatived.

In 1843, Klencke induced extensive tuberculosis of the lungs and liver in rabbits by inoculation with portions of miliary and infiltrating tubercle from man, but he did not push his conclusions home.

In 1865, Villemin made numerous experiments with suitable control-experiments, and seemed to have clearly demonstrated the infective nature of tuberculosis. He placed tubercular material beneath the skin of rodents, and general tubercle developed; he believed, therefore, that tuberculosis was a disease due to a specific poison contained

in the foci of the disease. His experiments were repeated by Cohnheim and Fränkel, Wilson Fox, Sanderson, and others, who found that tuberculosis could be induced, not only by the inoculation of cheesy material which was not tubercular, but also by inducing simple inflammation by the insertion of setons, of vaccine virus, bits of cork, paper, etc. Sanderson, however, concluded that nothing induced tuberculosis with such certainty as material taken from an undoubtedly tubercular source.

Klebs pointed out the possibility of the contamination of the supposed simple material by tubercular, for at that early date precautions were not very stringent. It is probable, too, that in many cases, where septic materials were used, the process induced was pyæmic.

In proof of the truth of Klebs' objection, Cohnheim failed to obtain positive results with non-tubercular material in Kiel and Breslau, his previous experiments having been made in the pathological institute at Berlin; and Fränkel also failed in a private house in the same city. Then, in a moment of inspiration, as Koch says, Cohnheim and Salomonsen[1] selected the anterior chamber of the rabbit's eye as the point of inoculation. Here the results of the inoculation could be watched from day to day, and, as primary spontaneous tuberculosis of the iris has never been seen in rabbits, the possibility of this could be excluded. It was thus proved that whilst inoculation of non-tubercular material into the anterior chamber of the eye failed invariably to induce tuberculosis, the inoculation of tubercular material produced tubercles in the iris and in the body at large a little later. The proof of the infective nature of the tubercular process was absolute, and it was further shown that tubercular materials from widely different sources contained the same virus. Tappeiner caused dogs to inhale, daily for fourteen days, 6 grammes of tubercular sputa delivered during six hours from a spray into a narrow box containing the animal: all became tuberculous, the twenty-third day being the earliest upon which tubercles were found. These and other facts caused many to regard tubercle as a specific infectious disease; Cohnheim adopted the view warmly,[2] and really sketched out the etiology of the disease (Koch).

Many of those who held this belief suspected that the virus was a vegetable parasite and searched for it. Klebs,[3] Schüller,[4] and Tous-

[1] *Virchow's Archiv*, lxxxii. p. 355.
[2] *D. Tuberkulose v. Standkunkt d. Infectionslehre*, 1879.
[3] *Prag. med. Wochschr.*, 1877. [4] *D. Skroph. u. Tuberk. Gelenkleiden*, 1880.

saint,[1] cultivated a coccus form from human tubercle, and produced tuberculosis by inoculation of animals with it. Schüller found these cocci in chronically inflamed synovial membranes and lupus-tubercles.

Aufrecht[2] stated that the centres of tubercles consist, not of caseous material, but of cocci singly and in chains, and of narrow rods, half as long again as broad, and closely resembling anthrax bacilli in appearance, stained by fuchsine (in too weak a solution to stain Koch's bacillus).

The next publication was Koch's paper.[3] By a special process of staining he first demonstrated the constant presence of peculiar bacilli in 11 cases of acute tuberculosis, 12 of cheesy broncho-pneumonia, 1 of tubercular nodule in the brain, and 2 of intestinal tuberculosis in man: 10 cases of perlsucht, and cases of spontaneous tubercle in monkeys and other animals, were investigated with a like result; and finally the bacilli were found in a large number of rodents and five cats artificially infected. As proving that the tuberculosis resulted from the inoculation, and was not accidental, we have the invariable coincidence: the more rapid development of the artificial than of the spontaneous tuberculosis; the early infection of the glands nearest the seat of inoculation, whereas the bronchial glands usually enlarge first in spontaneous disease; and, lastly, control-experiments in which animals were treated exactly as inoculated animals were, but no *living* bacilli were introduced and no tuberculosis occurred.

Finally, the bacilli were cultivated at 37°–38° C. in blood-serum sterilized and rendered solid by a special process; after passing through many flasks, these bacilli, suspended in distilled water and injected, produced tuberculosis as surely as the original material.

These results have been fully confirmed, especially by Cheyne,[4] and there is now no doubt but that they are absolutely true.

With regard to the cocci found by previous observers, they have not been found by the most eminent workers in the field of micro-organisms except in cases of "mixed infection"—*i. e.* cases in which both tubercle-bacilli and cocci have been inoculated upon the same individual; and Cheyne, who obtained material from Toussaint for a

[1] *Comptes rendus*, 1881. [2] *Path. Mittheil.*, 1881.

[3] "D. Ætiologie d. Tuberculose," *Berl. klin. Wochschr.*, No. 15, 1882. His paper on the same subject in the *Mittheil. aus dem Gesundheitsamte*, vol. ii., 1884, translated in the New Syd. Soc., "Micro-parasites in Disease," is fuller, and should be read by all.

[4] *Practitioner*, April, 1882.

full investigation of his results, was unable to confirm them in th slightest degree. On the contrary, Koch's *B. tuberculosis* was th only organism he could demonstrate in tubercles artificially induce by Toussaint.

We are therefore justified in believing that *B. tuberculosis* is th cause of all tubercular processes. Its presence, at least in the earl stages, rather than any anatomical structure, must be the essenti characteristic of tubercle.

Characteristics of the Bacillus.—The bacillus is 2–6μ long, ve thin ($\frac{1}{5}$–$\frac{1}{6}$ length), motionless, rounded at the ends, and generally appe beaded—clear spots (four to eig alternating with stained pa They are usually straight, may be curved; they occur sin but sometimes in pairs. Multi cation is very slow, and ta place by division and by sp formation. As a rule, they found in the cells of the tuber le, especially giant-cells. They are well shown in the accompany ng drawing, made from a speci en kindly lent me by Mr. Watson Cheyne (Fig. 94).

FIG. 94.

Tubercle Bacilli in Giant-cell, from Tuberculosis of Horse. × 600.

Growing only at high temperatures (30°–41° C.), they proba ly do not multiply outside the body, but live a wholly parasitic life unlike anthrax bacilli, for example, which are only occasionally parasitic, multiplying in the body by fission only, and requiring to regain the outer air to complete their developmental cycle by spore-formation. But, although they cannot multiply, they can live for a long time external to the body, having been found by Fischer and Schill to retain their virulence after forty-three days in putrid sputum and after one hundred and eighty-six in the dry state—perhaps even longer when the bacilli contain well-developed spores. In putrid fluids they could not long hold their own against the rapidly-multiplying septic organisms, which are specially adapted for the ordinary conditions external to the body. It is in the state of "dust" that are most likely to meet with tubercle-bacilli in our surrounding and obviously this is the state in which they are most fit to cause fresh infection.

With regard to the **origin of the tubercle-bacillus** from

non-pathogenic form, although it would seem that this must have occurred at some time, no other bacterium, even under such favorable conditions as the bodies of rabbits and guinea-pigs present, has been found to develop any of the peculiarities of the tubercular organism. Nor are there at present any facts known as to circumstances under which the virulence of tubercular virus can be modified, increased, or attenuated: nearly two years' cultivation external to the body caused no change in the latter direction (Koch). We must conclude, therefore, that these tubercular bacilli at the present day never arise *de novo*, that they can multiply only in the body of man or some other animal, and that, consequently, the bacilli which cause a fresh infection come either directly or indirectly from some tubercular individual.

Obviously, all cases of tubercular disease in man are not equally suitable for **dissemination of the virus.** This may be eliminated with the sputum, the feces, the urine (in urinary tuberculosis), and discharges from tubercular ulcers and abscesses; but only the first source is likely frequently to lead to infection. When, however, we consider that about one-seventh of mankind die of phthisis, and that in all cases in which cavities form the patients for weeks or months are expectorating large quantities of bacilli, we see that this one source is capable of keeping up an ample supply. The bacilli expelled by cough with small particles of mucus may be directly inhaled by the healthy; but sputum, which dries upon handkerchiefs, bed-clothes, and woollen garments, thence to be detached as dust, appears to be the most fertile source of infection. Bacilli found in the air are usually adherent to some bit of vegetable fibre, hair, or epidermis. Tubercular disease in animals does not seem to be a frequent source of infection to man. They produce no sputum, and few or no bacilli are expelled from their lungs. Bacilli are not frequent in their excreta. The milk of tubercular animals may give rise to infection; but as it contains bacilli only when the mammæ are tubercular, and as this is not often the case, milk is probably not a very frequent source of the disease in man. Lastly, there is the possibility of infection through the alimentary canal from eating tubercular meat. This can undoubtedly occur, as has been proved by feeding animals on tubercular flesh; but many things militate against its occurrence in man, in whom primary intestinal tuberculosis is not at all common. The flesh, if visibly diseased, is usually rejected; it is usually raised above 100° C. before being eaten; the disease in animals used for food, and especially in cattle, is usually localized, and infection could follow only upon

eating the tubercular lungs, glands, etc.; and lastly, the intestinal canal is not a favorable point of attack. The domestic animals are therefore sources of danger, and, unless proper precautions are taken, may become sources of infection; but in the great majority of cases the bacilli are carried from man to man.

The indications as regards prophylaxis which may be drawn from the above paragraphs are too plain to require categorical statement.

The bacilli are destroyed by boiling, by perchloride-of-mercury solution, and carbolic acid; but they resist the action of a 1 : 1000 solution of the perchloride and a 5 per cent. solution of carbolic acid for some minutes.

Modes of Entry of the Bacillus into Body.—The sound skin would seem to be quite impassable, and but few cases in which infection through wounds has occurred have been recorded. One of the most conclusive is the following: A perfectly healthy woman, with no tubercular history, cut her finger with a broken vessel containing sputum swarming with bacilli: some acute inflammatory symptoms subsided under carbolic fomentation, but a small subcutaneous nodule of granulation-tissue developed, and was removed at the end of a month, the wound healing *per primam*. Then came pain in bending the finger, and swelling extending along the tendon into the palm, also two swollen glands above the elbow and two in the axilla. All these parts were completely removed, the wounds healed at once, and no further spread took place. The tendon-sheath was full of granulation-tissue containing numerous tubercles; the glands were simply hyperplastic. Bacilli were fairly common in both. Riehl and Paltauf[1] have recently stated that dissecting warts are tubercular, because they found tubercle-bacilli constantly in giant-cells in degenerating nodules in the skin. Karg simultaneously made the same observation. Riehl and Paltauf regard the warty, inflamed papillæ as resulting from a mixed infection, cocci having been inoculated with the bacilli. I have lately treated two which followed upon wounds of the fingers during a post-mortem in a case of acute tuberculosis, but unfortunately the "warts" were lost. Volkmann examined one case of scrofulous eczema, and discovered the bacillus of tubercle in the epithelial and other cells: he therefore believes these catarrhs of the skin, and the even more frequent catarrhs of mucous membrane, to be due to the irritation of this organism. Certainly, lesions of this kind lead to the development of strumous glands; and in order to

[1] Kaposi, *Hauptkrankheiten*, 3d ed., p. 789.

account for the apparently primary enlargement of superficial glands Koch puts forward the now generally-accepted view, that the swelling has really been preceded by some scratch or slight sore (on the skin, whence lymphatics pass to the gland) upon which tubercular bacilli have fallen, and whence they have been conveyed into the lymphatics too speedily to interfere much with healing. Lastly, tuberculosis is said to have been conveyed by vaccination. The evidence is of the usual *post-hoc* kind, and the statement has probability against it, for the blood of tubercular animals is infective only in the most acute cases of general tuberculosis.

The mucous membranes—pulmonary and digestive—must therefore ordinarily afford passage to the bacilli: the possibility of this has been demonstrated by the success of inhalation-experiments with tubercular sputa and cultivations and of feeding-experiments with tubercular tissues. Pulmonary tuberculosis being much more frequent than intestinal, we may assume that bacilli more often pass into the tissues through the pulmonary than through the alimentary mucosa. The difficulties in both cases are considerable. As regard the lungs, the bacilli are drawn most deeply into the lungs by deep inspirations through the open mouth. Evidently, they cannot be carried beyond the regions of the tidal and complemental air, and will therefore be deposited in the smaller bronchi; but they multiply so slowly that they are usually expelled by ciliary action and coughing before they can seriously injure any spot and effect an entrance. To enable them to do this, specially favorable circumstances are necessary, such as the removal of much of the bronchial epithelium (after measles), the presence of bronchitis with tenacious—and therefore retained—secretion, the existence of adhesions of the lung or of a badly-formed thorax preventing full expansion of the lung and leading to local retention of secretions. Primary intestinal tuberculosis (which would occur from tubercular food) is rare; but ulceration of the bowels occurs about once in every three cases of phthisis, being apparently due to infection of the mucosa by the bacilli in swallowed sputum. Koch says that the intestinal mucosa offers a less favorable point of attack than the pulmonary—that the adult bacilli, like anthrax-bacilli, are probably all destroyed in the stomach, whilst the spores escape; so only spore-bearing bacilli can infect the bowel, and these only on condition that they are not hurried through the canal. Lastly, it seems that, just as a superficial gland may be infected from some lesion of the skin so slight as to escape notice and to leave no trace,

the bronchial and mesenteric glands—the former with especial frequency—may be infected by bacilli which pass through their respective mucosæ without leaving any permanent trace of their passage: instead of settling in the pulmonary or intestinal tissue, they are evidently carried on in the lymph-stream and arrested in the nearest gland, which enlarges, caseates, and often infects others. Such caseous glands act as reservoirs of bacilli and their spores, and too often prove sources of more or less widespread infection.

Having no power of locomotion, the tubercle-bacilli must be carried through the pulmonary muscosa by leucocytes, like the carbon-particles: in the intestines perhaps carriage may be unnecessary, and they may go through with the food-current.

Predisposition.—Nothing is more certain than that individuals vary in their liability to tubercular diseases, which are far more common in the young than in the old, and run most markedly in families. We have no knowledge of what constitutes this predisposition, which may be inherited or acquired, and, apparently, quite local or very general. A small, flat chest and a tendency to catarrh are often present in people who ultimately develop phthisis, and the absence of free respiratory movements is often held to favor the entry of the bacillus; often, too, members of tubercular families are specially exposed to infection in nursing a sick member; but in our present state of knowledge it seems impossible to believe that the difference between the predisposed and the immune is that in the latter the bacilli do not enter: it seems much more probable that they do enter in small numbers, and are speedily destroyed by the tissues. How can we explain acute meningeal tuberculosis or tuberculosis limited to the peritoneum—in both of which multitudes of bacilli must have been thrown into the circulation from some bronchial gland or other focus—unless we assume that the bacilli could not develop elsewhere than in the meninges or peritoneum respectively?[1] How, too, should we otherwise explain the recovery of some people from phthisis, except by assuming that the soil, which was favorable to the growth of the bacillus originally, has, in some at present unknown way, become unfavorable? The predisposition seems to vary distinctly from time to time in the life of the individual.

[1] It is possible that a single infection of the pleura, pericardium, or peritoneum might be spread more or less rapidly over the whole membrane through its lymphatics and by means of the movements of the organs. It is difficult to conceive an infection of both Sylvian arteries and spread against the lymph-stream from the base to the convexity of the brain.

Development in the Tissues.—Having found a spot in which it can grow, the bacillus proceeds to multiply: most bacilli are taken up by cells which enlarge into giant-cells and become the centres of typical "tubercles" (p. 301). The presence of these tissues excites more or less inflammation, often so much that we find the tissues diffusely infiltrated, distinct nodules being scarce or absent (**infiltrating variety**). Caseation at the non-vascular centres soon follows, being preceded by coagulative necrosis of the cells—due, no doubt, to the baleful influence of the bacilli. The nearest lymphatic glands often become affected. The primary lesion may become localized, as before explained (p. 309), or extension to other parts may occur from it.

Modes of Spread.—(1.) **By "Continuity of Tissue" and by Lymphatics.**—This is the way in which the masses of conglomerate yellow tubercle are formed, and similarly patches of infiltrating tubercle, say of the skin—"scrofuloderma"—spread. It is supposed that leucocytes enter the primary focus, take up a bacillus or a spore, and wander out again along fine lymphatics into the surrounding tissues, there to sicken and swell into a giant-cell not far from the parent mass, into which the fresh tubercle falls as it enlarges and caseates. The young tubercles form the grayish translucent ring round the conglomerate mass (p. 301), with here and there an offshoot of slight length. But occasionally a leucocyte containing a bacillus finds its way into the lymphatic, and is carried by the lymph-stream to the nearest gland. The situation being a favorable one for observation, the process of infection of mesenteric glands from an intestinal ulcer may sometimes be traced by tubercles along the track. Ponfick has described, as not very uncommon in cases of acute tuberculosis, tubercles in the thoracic duct; these he regards as evidence that the virus had passed by this channel to the blood.

(2.) **By Veins.**—Mügge[1] described tubercular infiltration of the walls of pulmonary vessels, especially veins, in pulmonary tuberculosis; and Weigert[2] believes that this actual growth of the bacillus into the circulation is frequently the source of general infection.

(3.) **By Arteries.**—In a cheesy bronchial gland from a case of acute tuberculosis Koch found the wall of an artery, which was still pervious, similarly infiltrated; and he believed this to be the source of general infection. In another instance Cheyne was equally fortunate.[3]

[1] *Virchow's Arch.*, vol. lxviii. p. 242. [2] *Ibid.*, vol. lxxvii. p. 269.
[3] *Loc. cit.*, p. 292.

In one or other of these ways, or perhaps in all of them, the virus reaches the blood and is carried all over the body, developing when and where the conditions are suitable—in the lungs, meninges, etc. If the supply of virus is plentiful the case is likely to be most acute. Laennec used to teach that the tubercles appeared in crops, distinguished by the amount of degeneration they had undergone. This would indicate an intermittent supply.

(4.) **By Infection of One Part from Another.**—Examples of this are easily found. Perhaps the best is easily seen when a sudden inspiration occurs upon the bursting of a tubercular focus into a bronchus, and draws the infective material into many other bronchi, with the result that a caseous pneumonia develops, beginning in the numerous patches of "racemose tubercle"—*i. e.* the tubercular tissue is moulded into racemose forms by the alveoli in which it grows. Other examples are the infection of the palate from the tongue, of the intestine from swallowed sputum, and of the lower urinary tract from the kidney.

Results of Extension.—An acute miliary tuberculosis of the meninges, lungs, peritoneum, and various abdominal viscera plainly implies that a large number of bacilli have found their way within a short space of time into the blood: the result is just such as follows the intravenous injection in rodents of a syringeful of a pure cultivation of the bacilli. As it is inconceivable that bacilli in such numbers could be absorbed so rapidly through a mucous membrane into the blood, it is necessary to assume the existence of some primary focus where bacilli have multiplied, and have at last gained an entrance to the blood-stream by one or other of the above-mentioned routes. The pulmonary mucous membrane being that through which bacilli commonly pass into the system, the focus in which this multiplication occurs and whence generalization usually takes place is a caseous bronchial gland; generally there is evidence of tubercular disease of one or both lungs also, which may be active or completely quiescent. But acute miliary tuberculosis may spread from any localized focus, primary or secondary, wherein there are living bacilli. Extension by means of any lymphatic vessel can lead only to the formation of tubercles along this vessel or in glands through which the lymph passes, unless the thoracic or right lymphatic duct be affected, in which case the organisms may find their way into the systemic veins. They would then pass first through the lungs; but they are of such small size that there could be no difficulty in their

passage through the pulmonary capillaries to those of the systemic circulation.

We have spoken of acute general miliary tuberculosis, using the term in contradistinction to a localized tuberculosis—*e. g.* a mass of conglomerate tubercle in the brain or a caseous gland. But even a "general" tuberculosis, due apparently to the casting of numbers of organisms into the blood, is far from general, the lungs, spleen, and liver being very frequently, the voluntary muscles and mammæ (p. 302) very rarely, affected; and we pass insensibly from the most widespread miliary tuberculosis, through cases of miliary tuberculosis limited to the meninges or peritoneum, through cases of multiple infiltrated tuberculosis (practically, numbers of miliary tubercles imbedded in granulation-tissue in a limited area) of glands, skin, bones and joints, to the case in which only one spot of skin, one joint or gland, seems to be affected.

As we have before said (p. 318), the selection of special organs in "general" tuberculosis seems to indicate special **predisposition** on the part of these organs: there is no reason to assume that the bacilli are arrested in them, and not in other parts. The same explanation would appear applicable to cases of limited miliary tuberculosis, and may possibly be the reason why tubercular meningitis affects the base, rather than the convexity, of the brain. Again, there seems no other explanation to offer of what seems to be a well-established clinical fact—viz. that children who suffer from multiple lesions of skin, glands, bones and joints do not develop visceral tuberculosis nearly so often as those in whom one joint is affected.

Next, with regard to the **dose of organisms**: this may conceivably vary from a large number thrown into the circulation at once to a few or even a single bacillus; and between these extremes there may be repeated moderate or small doses from the same or from different foci, giving rise to the successive "crops" of tubercles to which Laennec drew attention, the more recent being small and gray, and the older larger and yellow. When only a few bacilli at a time enter the circulation, the infiltrations which they excite reach a larger size than they could possibly attain in the speedily fatal general cases. Many of the cases in which single glands are affected are doubtless due to infection from small wounds or tubercular sores of skin or mucous membrane from which they obtain their lymph-supply. But many cases of localized tuberculosis, especially of bone and joint, admit of no such explanation: these Koch believes to be due to the entry

into the circulation and lodgment in the affected part of a single bacillus; and he thinks that in these cases, as in those of widespread infection, the organism is obtained from some primary focus, usually a bronchial gland, whence it has, as it were accidentally, slipped by the lymph-path into the blood. He thinks it highly improbable that even a single organism could pass into a lung-capillary from an alveolus without causing a tubercular focus in the lung itself.

The **seat of infection** may not be without its effect in explaining some peculiarities of the disease, and should be borne in mind. As to **heredity,** tubercle, unlike syphilis, very rarely extends from the parent to the fœtus *in utero;* and Koch found that guinea-pigs pregnant at the time of infection or becoming so soon after did not transmit the disease to their young.

It is impossible to explain why some tubercular processes remain local, whilst others generalize. Blocking of lymphatics, non-invasion of the walls of blood-vessels, feeble local growth of the bacillus, healthy resistance on the part of the tissues in general, may afford hypothetical explanations.

Although in the great majority of cases of acute tuberculosis a primary cheesy focus is found, it will have been gleaned, especially from Koch's experiments with pure cultivations, that *caseation has nothing whatever to do with the production of the tubercular virus.*

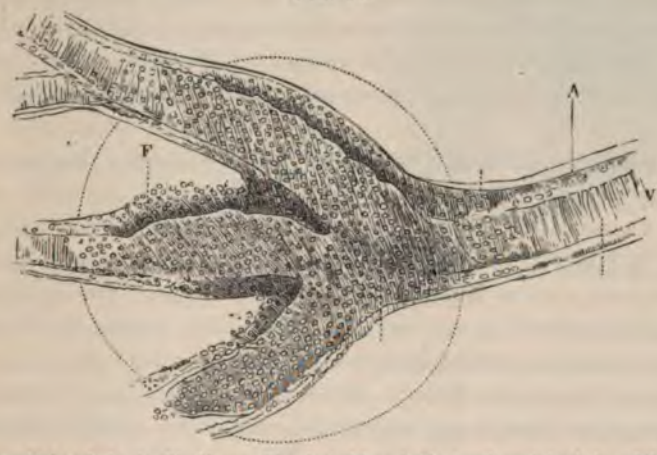
Tuberculosis of the Pia Mater and Brain.

TUBERCULAR MENINGITIS.—In the pia mater the tuberculous process is associated with inflammation of the meninges and superficial parts of the brain, constituting the condition known as **tubercular meningitis** (really meningo-encephalitis). This is almost invariably a part of a general tuberculosis.

The process is almost exclusively confined to the pia mater at the base of the brain, and the tubercular nodules—which may easily escape observation—are seen in connection with the small arteries in the Sylvian fissures and deeply seated between the convolutions. A few scattered granulations are, however, frequently visible on the upper surface of the hemispheres. (To see the tubercles, tear out the Sylvian arteries with their branches, float them in water, and spread them out on a glass plate; examine over a dark background.) The inflammatory growth originates in the perivascular lymphatic sheaths which enclose the small arteries of the pia mater (Fig. 95), and, the

cellular infiltration commencing at separate centres, numerous small gray nodules are produced around the vessel. These, which are distinctly visible to the naked eye, cause an external bulging of the

FIG. 95.



Miliary Tubercle in the Pia Mater: The dotted line indicates the original size of the tubercular nodule. A. The lymphatic sheath. V. The blood-vessel. F. Elements within the sheath. × 100. (Cornil and Ranvier.)

sheath and a diminution in the calibre, or even complete obliteration, of the enclosed vessel.

The localized obstructions to the circulation which result from the pressure of the perivascular nodules increase the hyperæmia at the base of the brain, which thus becomes exceedingly vascular, there being in some cases rupture of the vessels and extravasation. A fibrinous transudation takes place from the hyperæmic and injured vessels, blood-corpuscles escape, and thus the meshes of the pia mater become infiltrated with a sero-fibrinous or puriform liquid which tends to collect specially in the grooves between the convolutions. The subarachnoid fluid is increased in quantity and turbid: pressure within the dura mater rises steadily.

These changes in the pia mater at the base of the brain are attended by hyperæmia, infiltration with leucocytes and fluid, and softening of the subjacent cortical substance, accounting for the early delirium and hypersensitiveness of the special senses. The ependyma and choroid plexus also become exceedingly vascular, and the walls of the ventricles, together with the fornix and soft commissure, soften. The lateral ventricles become distended with serum progressively

(*acute hydrocephalus*), so that the convolutions on the surface of the hemispheres are found pressed against the skull and flattened. All trace of fluid is driven from the subdural space and the arachnoid is dry and sticky.

The insensibility, deepening into coma, which precedes death is accounted for by the rise in intracranial pressure and by the injury done to the cells of the cerebral centres by the inflammatory process and by the prolonged high pressure to which they are subjected.

TUBERCULOUS MASSES IN THE BRAIN.—Large masses of conglomerate tubercle (p. 301) are occasionally met with in the brain unassociated with any general tuberculous process, and, curiously, in spite of their often considerable size, they rarely give rise to symptoms such as might indicate their pressure. The explanation is that their growth is very slow, and other cells assume the functions of those destroyed, whilst fresh conducting paths are opened up, compensation being thus effected. These masses, which vary in size from a hazel-nut to a hen's egg, commonly occur in the cerebral substance, especially at the base of the brain. They are of a pale-yellow color and firm consistence, and usually form quite round globular tumors. Their surface is often seen to be covered with minute gray nodules, which extend into the surrounding tissue; and on section similar nodules are sometimes visible scattered through the substance of the tumor. In most cases only one or two such masses are found, but occasionally they are more numerous. They occur especially in childhood. When examined microscopically they are found to be made up of numbers of distinct tubercles, all of which, except those near the margin of still extending masses, have undergone fatty degeneration. Near the edge, where the structure of the tubercle is recognizable and typical (p. 302), compressed or obliterated blood-vessels may be seen. Attention has already been drawn to the locally and generally infective nature (p. 317) of these masses.

Tuberculosis of Lymphatic Glands.

In the lymphatic glands tuberculous processes give rise, in the first place, to changes in the cortical portions of the gland (Treves), inasmuch as it is with these that the infective material which is conveyed by the lymphatic vessels first comes into contact (Fig. 96). In the earlier stages of the process small pale-gray nodules are often visible

scattered through the warmer-colored (vascular) cortex. These gradually increase in size and become caseous. The gland meanwhile becomes enlarged by the addition to its substance of the "tubercles" (which gradually spread in along the lymph-sinuses to the medullary portion), with their surrounding halo of round-celled infiltration; and consequent upon the infiltration and filling up of the lymph-sinus the distinction between the medullary and cortical portions is lost, and the section presents a grayish homogeneous surface on which are varying-sized tracts of caseous material. The cell-infiltration frequently undergoes marked fibroid development and the capsule thickens, so that the caseous masses are surrounded by a dense fibroid structure. The whole gland is often ultimately converted into a caseous mass. The caseous portions of the gland may subsequently soften, dry up, or calcify.

FIG. 96.

Tuberculosis of a Lymphatic Gland. The earliest stage of the process, showing the giant-cell. × 200.

Not uncommonly, no "tubercles" are visible, and the surface of section in the early stage has a more pulpy, swollen appearance, and may be distinctly more vascular, than normal: microscopically, a round-celled infiltration, with few large cell-forms, is found. The result of the infection has been a more acute and diffuse inflammation than that above described. Caseous patches and fibroid changes ultimately appear.

As before stated, the affection of lymphatic glands is usually distinctly secondary to a tubercular inflammation in the area whence they draw their lymph; sometimes it *appears* to be primary, bacilli having entered through mucous membrane or skin without exciting any marked inflammation. The glands most commonly affected are the bronchial, mesenteric, and cervical groups.

TUBERCULOSIS OF MUCOUS MEMBRANES.

The alimentary, the urino-genital, and the respiratory mucous tracts may all be seats of tubercular infiltration and ulceration: it is extremely probable that some catarrhal affections of the tonsils and

pharynx, of the Eustachian tube and middle ear, and of the intestine are due to the irritation of the tubercular organism.

Tubercular ulceration or fissure of the lip, usually with marked thickening, is not uncommon in children and young adults. On the tongue and pharynx tubercular ulceration is rare, and is usually secondary—at least in point of time—to phthisis. The occurrence of tubercles in the œsophagus and stomach is very rare, but apparently clear cases have been described. The course, the microscopic and naked-eye anatomy, of all these ulcers being the same, we shall describe them under the heading of "Intestine," in which section of the alimentary tract they are by far most common.

THE INTESTINE.—Tubercular ulceration of the intestine is rarely primary, being then due most probably to infection from tubercular milk or meat; as a rule, it is secondary to phthisis, of which it complicates one-half to two-thirds of the fatal cases, and the infection arises from the swallowed sputa (p. 315). Small and large bowel are said to be affected with about equal frequency, and both suffer much oftener than one. The morbid process begins in the solitary and agminated follicles, and is most marked where these are most numerous—viz. at the lower end of the ileum and in the cæcum: the appendix may be affected; also the duodenum and rectum.

The first stage of the process consists in a cellular infiltration of the structure, and some solitary glands and certain follicles (*not* all) of some Peyer's patches thus become swollen, and project unduly above the surface of the membrane. The new elements then undergo fatty changes and soften, the degeneration in Peyer's patches commencing at several separate centres, over which the mucous membrane gives way, and often by the breaking-down of fresh tubercles at the margin until the whole patch becomes destroyed. As the result of these changes an ulcerated surface is produced, the floor and edges of which are more or less thickened, owing to the extension of the infiltration into the surrounding tissues. This thickening, together with increased vascularity and the presence of actual tubercles in the serous and subserous tissues, enables us to localize the ulcer before the bowel is opened. In the floor of the ulcer, formed usually by the submucous, sometimes by the muscular, and rarely by the peritoneal coat, small tubercles are developed, principally around the blood-vessels, and, as these are arranged transversely around the intestine, the new growth proceeds in the same direction. These nodules also soften and become

caseous, and thus the process of ulceration gradually extends transversely until the whole circumference of the gut may be destroyed (*annular ulcer*). By the blending of adjacent ulcers most irregular figures are formed, and in extensive cases mere islets and bands of mucous membrane only are left in wide areas of the bowel. The ulcers thus produced present a strong contrast to those of typhoid. The edges and base are thickened and indurated, and the tuberculous nodules, tending to become caseous, are seen scattered in its floor and

FIG. 97.

A Tubercular Ulcer of the Intestine (diagrammatic): *a*. Epithelial lining; *b*. Submucous tissue; *c*. Muscular coat; *d*. Peritoneum.

beneath its margin (Fig. 97). Bacilli are usually numerous, and may be recognized in the stools by suitable staining.

The tubercular ulcer rarely, if ever, heals entirely; but ulcers may heal in parts while they spread at others, and the contraction of the scar, and when no scar forms of connective tissue in which the tubercles are imbedded, may lead to marked narrowing of the gut. Owing to the thickening of the tissues at its base, perforation is quite an exceptional occurrence, and it takes place far more commonly into a neighboring viscus, to which the ulcer has become adherent, than into the peritoneum.

The lymphatic glands in connection with tubercular ulcers are generally affected, and one can often see the lacteals leading from the ulcers, and even the thoracic duct, irregularly swollen by tubercles.

THE RESPIRATORY TRACT.

The larynx and trachea both suffer from tubercle in its miliary and infiltrating forms, the former much more often than the latter.

TUBERCLE OF THE LARYNX (Laryngeal Phthisis) may be primary, but is often secondary to disease of the lungs. It is said to commence as subepithelial granulations situate chiefly in the ary-epiglottid folds, on the cords, and on the under surface of the epiglottis. These may be few or numerous, and may ulcerate early—especially on the cords—or may multiply and run together into a diffuse infiltration, which in the ary-epiglottid fold produces a pear-shaped swelling with

its large end toward its fellow in the mid-line. Spreading ulceration ultimately occurs, perhaps leading to the formation of abscesses and necrosis of cartilage, to hectic exhaustion, and death.

TRACHEAL ULCERS are usually superficial, and may rarely be very extensive.

TUBERCULOSIS OF THE LUNGS (Acute Miliary).—Tuberculous processes occur in the lungs as a part of a general tuberculosis, and also in pulmonary phthisis. The nature of the resulting inflammatory lesions is similar in both. It will be well, however, in the present place more particularly to describe these lesions as they occur in the general infective disease. The more limited processes which take place in phthisis will be again referred to in a subsequent chapter devoted to the consideration of this affection. (See "Pulmonary Phthisis.")

The pulmonary lesions met with in general tuberculosis consist, for the most part, of disseminated nodular growths, which are universally known as miliary tubercles. These growths are of two kinds—the **gray** and the **yellow.** The **gray** are semi-transparent nodules of a grayish-white color, varying in size from a small pin's head to a hemp-seed. They are somewhat spherical in shape, and usually possess a well-defined outline. Sometimes they are firm and almost cartilaginous in consistence, whilst in other cases they are much softer and almost gelatinous. These softer forms, instead of being semi-transparent, are more opaque and white. The **yellow** are, for the most part, larger than the preceding—many of them much so, some being as large as a pea. They are also softer in consistence, less defined and regular in outline, and they pass more insensibly into the surrounding tissue. Many of them possess a grayish-white translucent margin, which may be pretty firm in consistence, but never so hard as are many of the gray nodules, whilst their central portions are opaque, yellowish, or caseous.

Both the gray and the yellow nodules are often found associated in the same lung; in other cases the gray nodules only are met with; whilst, less frequently, nearly all the growths are of the yellow variety. The condition of the pulmonary tissue which is situated between the nodules varies considerably. It may be perfectly normal, more or less congested and œdematous, or it may present varying-sized tracts of grayish, granular, friable consolidation. A perfectly normal condition of the intervening pulmonary tissue is found in many of those cases in which all the growths are of the firm, gray variety; but when

there are numerous yellow or soft gray nodules the lungs are nearly always more or less congested or consolidated. Although the virus is distributed by the circulation, the tubercles are usually present in greatest number at or near the apex, like the lesions in ordinary phthisis.

When these nodules are examined microscopically they are seen to exhibit two different kinds of structure—viz. the lymphoid structure with giant-cells, which has been already described as that which is the most characteristic of tuberculous lesions, and accumulations of epithelial cells within the pulmonary alveoli (catarrhal pneumonia). There is, however, this marked difference between the various kinds of nodules: that whereas the small firm gray ones are constituted almost entirely of the first-named structure, the larger soft gray and most of the yellow ones consist largely of the intra-alveolar accumulations.

Firstly, with regard to the soft gray and yellow nodules. Most of these when examined with a low magnifying power present the appear-

FIG. 98.

A Small Soft Gray Tubercle from the Lung in a Case of Acute Tuberculosis: The whole of the tubercle is shown in the drawing, and it is obviously constituted largely of *intra-alveolar* products. × 100, reduced to ⅕.

ance represented in Fig. 98, the nodules evidently consisting largely of accumulations within the alveolar cavities. When more highly magnified their constitution becomes more apparent. It is then seen that the alveolar cavities are filled with epithelial elements and small cells

resembling leucocytes, whilst the alveolar walls are more or less extensively infiltrated and thickened with lymphoid cells (Fig. 99). In many cases the central portions of the nodules will be seen to have undergone extensive degenerative changes, and to consist merely of a structureless granular débris, so that the accumulations within the alveoli and the cellular infiltration of the alveolar walls are visible only at their periphery. This is always the case in the distinctly yellow tubercles (Fig. 100).

FIG. 99.

A Portion of a Small Soft Gray Tubercle from the Lung. This is from a case of acute tuberculosis, probably in an earlier stage than that from which Fig. 98 was drawn. The figure shows one of the alveoli filled with epithelial elements and a few small cells, with some cellular infiltration of the alveolar wall. × 200.

The histological characters of the firmer gray nodules differ somewhat from the preceding. In these the cellular infiltration and thickening of the alveolar wall is much more marked, and many of the

FIG. 100.

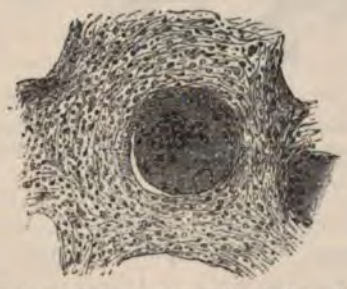
A Portion of a Yellow Tubercle from the Lung in a Case of Acute Tuberculosis, showing the degeneration of the central portions of the nodule, *c*, and the cellular thickening of the alveolar walls and accumulations within the alveolar cavities at the periphery, *p*. × 100.

alveolar cavities are occupied by giant-cells, originating, according to Dr. Klein,[1] by fusion of the alveolar epithelium or by excessive devel-

[1] *Loc. cit.*

opment of one epithelial cell. Since the publication of Dr. Klein's statement I have frequently observed these cells situated distinctly in the alveolar cavities, and I have little doubt they originate in the way he describes (Fig. 101). In other cases the alveolar structure has completely disappeared, and the tubercle, when examined with a low magnifying power, appears as a little somewhat spheroidal mass, the cellular elements of which are seen to be grouped around separate centres (Fig. 102). When more highly magnified these centres are seen to correspond with the giant-cells already described and the small-celled structure grouped around them, as is well shown in Fig. 101. This is a fully-developed tubercle of the lung. The small-celled structure at the peripheral portions of the nodules extends into and

FIG. 101.



A Portion of the More External Part of a Gray Tubercle from the Lung in a Case of Acute Tuberculosis, showing the extensive infiltration and thickening of the alveolar walls, and the giant-cells within the alveolar cavities. × 100.

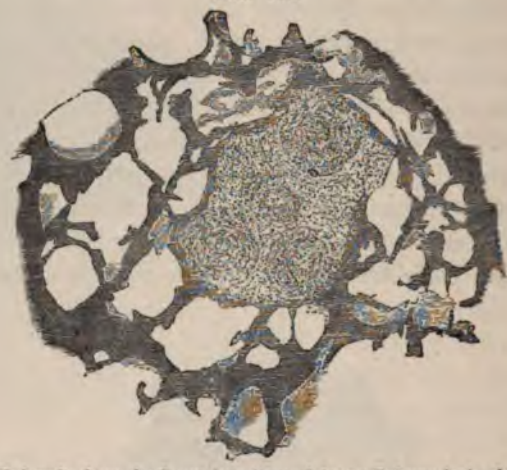
produces a thickening of the walls of the alveoli with which the nodule is incorporated (Fig. 103). In the tubercles thus constituted extensive retrogressive changes rarely occur. Degeneration is slow and very incomplete, and the nodule often becomes imperfectly fibroid.

Respecting the cause of these differences in the histological characters of the miliary lesions in the lungs, I believe them to depend upon differences in the age of the nodules and in the intensity of the tuberculous process.[1] If the intensity of the process be considerable, the nodules will consist in the main of accumulations of epithelium within the pulmonary alveoli, and the nodule will rapidly undergo disintegration. (See Fig. 99.) If the process be less intense and the nodules attain a more advanced age, degeneration will be less rapid and

[1] Intensity comprises two factors—severity of injury and susceptibility of injured tissue. (See "Inflammation.")

complete, the cellular infiltration and thickening of the alveolar walls will be greater, and the epithelial elements may form large multi-

FIG. 102.



A Firm Gray Tubercle from the Lung in a Case of Acute Tuberculosis, showing the grouping of the elements around separate centres, the nodule consisting of several giant-cell systems. × 33.

nucleated cells. (See Fig. 101.) Lastly, in the least intense and most chronic processes the development of multinucleated elements and the formation of the network of branched cells reaches its maxi-

FIG. 103.

A Small Portion of the Most External Part of a Firm Gray Tubercle from the Lung in a Case of Acute Tuberculosis, showing the incorporation of the nodule with the alveolar wall, *a*. × 270.

mum (see Figs. 91 and 102), degeneration takes place slowly in the central portions of the nodule, and there is often considerable fibroid

induration of the new tissue. There is thus a close analogy between the tissue-changes resulting from tuberculosis of the lungs and those which result from other chronic inflammatory processes. (See "Chronic Inflammations.")

Lupus Vulgaris.

This disease is characterized by the appearance of reddish-brown nodules of granulation-tissue upon the skin (chiefly of the face), and much more rarely upon the mucous membranes of the conjunctiva, pharynx, vulva, and vagina. The tubercles are situate primarily in the corium, and at first are smaller than a pin's head, but they may reach the size of a pea; fresh ones appear at the periphery, whilst those in the centre blend into a more or less diffuse infiltration. The disease *appears* almost always between the age of two years and puberty, and is especially common in the obviously scrofulous: *recurrences* may occur again and again, and the disease may thus last, off and on, throughout a lifetime.

Structure.—The nodules consist of granulation-tissue containing epithelioid, and often a good many giant-cells. They differ from true tubercles in being *rather richly vascular*. The intercellular substance is scanty and homogeneous. It is not uncommon to find that long anastomosing processes of epithelium have grown down into the round-celled growth, the physiological resistance (p. 131) of which would seem to be less than that of normal corium.

Course.—Spread occurs by the production of fresh nodules at the margin of the primary focus. The course is always chronic. When the patch has reached a certain size it may undergo no change for a long time; the nodules and infiltration may end in degeneration and **absorption**, a white scar being left, or in **ulceration**. After eating away the tissues to varying depths, sometimes destroying large portions of the nose, lip, or eyelid, the ulcers may heal, or healing may go on at one point and destruction at another. There is little or no tendency to caseation, and glands rarely become affected.

Etiology.—The tubercle-like structure of the nodules caused Friedländer to surmise that lupus was a tuberculosis of the skin soon after the researches of Langhans and Schüppel had determined the structure of the typical tubercle. Hüter and Schüppel inoculated animals with lupus-tissue, producing a disease like tuberculosis, and Cohnheim and Fränkel obtained positive results by introducing bits of lupoid tissue

into the anterior chamber of the eye. Finally, Koch examined seven cases, and succeeded in demonstrating the presence of the tubercle bacillus in all—usually in giant-cells and very sparingly distributed, so that twenty to forty sections might sometimes be examined before a single bacillus was found; then two or three might appear in one section. In spite of the rarity of the bacilli, inoculation of rabbits or guinea-pigs gave positive results *in every case*—suggesting the possibility of the presence of spores where the adult organisms cannot be demonstrated. Lastly, a pure cultivation was obtained from one case which acted exactly like a cultivation of tubercle-bacilli from any other source.

We may add that the bacilli have been found in tubercles excised before ulceration has begun, and that many observers have demonstrated their presence, though rarely with absolute constancy, in a series of cases. Some scrofulous lesion is often present in cases of lupus, and it is asserted that patients suffering from lupus—perhaps even the majority of them—die of some tubercular disease; *e. g.* phthisis (Weinlechner) or meningitis (Dontrelepont).

The truth of the above is admitted by Kaposi, who nevertheless dissents from the view that lupus is a tuberculosis of the skin. His arguments against it are mainly that even the frequent coincidence of scrofula and lupus proves nothing; that the bacilli are strikingly few in number, and that *perhaps* the mode of staining is not really distinctive of the tubercle-bacillus; that tuberculosis always results from inoculation with lupus tissue—lupus never; that there is no evidence of the contagiousness of lupus; and, lastly, that lupus remains lupus throughout its course, and never passes into scrofuloderma and true tuberculosis of the skin.[1] This statement is contradicted by many observers, and none of the arguments touch the chief fact in the case—the *constant* presence of the bacillus or its spores, as shown by inoculation. Now, the constant presence of an organism in association with a specific type of disease is very strong evidence of an etiological connection between the germ and the disease, even though we cannot by inoculation produce the disease in other animals.

[1] *Hautkrankheiten*, 3d ed., p. 767.

CHAPTER XXXII.

SCROFULA.

THE constitutional condition known as scrofula is characterized[1] by a liability of certain tissues to become the seat of chronic inflammations, the causes of such inflammations being very slight and sometimes wholly hypothetical. It is generally believed that these tissues either possess congenitally or acquire as a result of abnormal conditions of life an enfeebled resisting power against injury. Virchow says their *vulnerability is excessive*. Consequently, the above slight or undiscoverable causes—injuries which would have no effect or only the most passing upon a healthy subject—produce inflammation in the scrofulous. In this way it is sought to account for the **abnormal susceptibility to inflammation.**

The explanation given of the **abnormal chronicity** of the processes is very similar. We know that chronic inflammation implies the prolonged or frequent action of a cause. It is almost impossible to put an inflamed part under such conditions that no cause of inflammation, as friction, pressure, tension, contact with a foreign body, etc., can affect it. These are not sufficient to keep up an inflammation in a healthy person, but in the vulnerable tissues of the scrofulous they are supposed to be able to do so; and doubtless they aid in rendering the process chronic.

This susceptibility, although more or less general, is commonly most marked in the mucous membranes and in the lymphatic glands, especially in those glands which stand in direct relation with the scalp, fauces, tonsils, and pharynx (cervical), with the lungs (bronchial), and with the intestine (mesenteric). It is to these, it may be remarked, that organisms are most likely to obtain access. The skin (eczema impetiginodes), bones, and joints (caries and chronic arthritis) are also very liable to be affected. The part which suffers varies in different cases, and *slight* injury (p. 278) is often the determining cause.

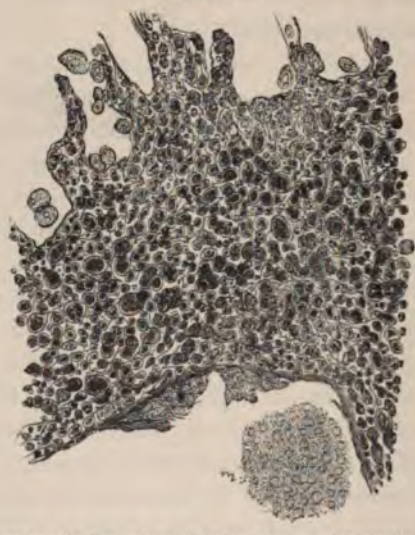
With regard to the tissue-changes occurring in scrofulous inflam-

[1] A special type of countenance and body has long been held to characterize the scrofulous diathesis (see works on medicine or surgery), but its scientific value is doubtful.

mation, it must be remembered that when inflammation occurs in a healthy individual, if it does not cause the death of the part, the inflammatory products either become absorbed or the process leads to suppuration or to the formation of a vascularized connective tissue. In scrofulous inflammation the absorption of the inflammatory products is very much less readily effected: they tend to **infiltrate** and **accumulate** in the tissue, where by their pressure they interfere with the circulation and so lead to retrogressive and **caseous** changes. There is little or no tendency to the development of new blood-vessels, and hence there is no organization of the new growth. These peculiarities are to be in great measure ascribed to that inherent low vitality of the tissues which obtains in this disease.

When we examine the tissues of a part affected by scrofulous inflammation, we usually find a diffuse cell-infiltration of them, and we notice here and there opaque yellow caseous spots and patches. Distinct

FIG. 104.



Scrofulous Inflammation of a Bronchus. Section of a small bronchus of a markedly scrofulous child, the subject of bronchitis, which terminated in miliary tuberculosis. The deeper structures of the bronchial wall are seen to be extensively infiltrated with cells, most of which are *larger* than those met with in the less extensive infiltration of healthy inflammation. The infiltration extends to and invades the walls of the adjacent alveoli, which are seen at the upper part of the drawing. The cavity of the bronchus contains a little mucus, *m*. × 200, reduced ½.

tubercles are often recognizable by the naked eye; and almost always the microscope reveals non-vascular collections of cells, arranged as in

typical tubercules—*i. e.* one or more central giant-cells surrounded by epithelioid cells, and these again by lymph-cells. Large cell-forms abound (Figs. 96 and 104). The whole infiltration contains but few vessels; hence the pale-purplish look of the granulation-tissue which lines a chronic ("scrofulous") abscess as contrasted with the vivid red, vascular layer round a focus of acute suppuration, the pallor about a scrofulous joint (*tumor albus*), and so forth. It is therefore evident that the anatomy of a scrofulous inflammation is that of the infiltrating form of tubercle (p. 301), and we need hardly point out that the course of a scrofulous inflammation—chronic, with but little tendency to resolution, organization, or suppuration, but with marked tendency to progressive infiltration, caseation, and often to softening (chronic abscess)—is precisely that which we see in tuberculosis of the lungs ("Phthisis," *q. v.*).

We must next note that scrofulous inflammations not uncommonly end in *acute miliary tuberculosis;* and in explanation of this it has been shown that the above-given histology of scrofulous lesions is due to the presence in the inflamed tissues of the Bacillus tuberculosis. The bacilli, though present only in small numbers in the more chronic cases, have frequently been demonstrated microscopically: pure cultivations have been obtained, and successful inoculations with these and with portions of diseased tissues have been performed (p. 309.) The proof would therefore seem complete that scrofulous lesions are tubercular, and that the "scrofulous diathesis" is really the tuberculous diathesis. It is well known that consumptive parents have scrofulous children, and *vice versâ.*

As to the excessive vulnerability or abnormal susceptibility to injury of the tissues which is supposed to exist, it appears to be reducible to this, that certain portions of tissue (many or few) in the scrofulous are excessively predisposed to suffer from the Bacillus tuberculosis. After amputations (infliction of serious injury) for strumous disease we count upon obtaining speedy union; the result of prolonged tearing and cutting operations upon diseased synovial membranes (erasion of joints, arthrectomy) is excellent, provided that something like completeness is attained in removing the morbid and morbidly-inclined tissue; the contents of scrofulous glands are scooped out daily, with the usual result that the inflammatory process subsides and spread to other glands ceases. No more rest to the parts or freedom from irritation is obtained for the wounded tissues after an arthrectomy than was given before; often, indeed, much less is obtained,

and sepsis may be added, and yet if the excision has been complete the parts do not again become the seats of intractable inflammation. And this is the case even when large portions of epiphysis, in which scrofulous joint-diseases frequently commence—and which therefore must be regarded as vulnerable in a high degree—are left. We may say, therefore, that the results of surgery leave little room for the doctrine of excessive vulnerability of tissues.

Against the view that scrofulous lesions are really tubercular, and that the scrofulous and tubercular "diatheses" are identical, has been urged the extreme frequency with which the mucous membranes and lymphatic glands in scrofulous children are the seats of obstinate and protracted inflammations which ultimately end in recovery. But we have already alluded to the slowness with which recovery even from phthisis has been recognized (p. 308): it is no essential part of a tubercular process that it should end fatally, as experiments on animals and observations upon man fully show. Some of the catarrhs aboye alluded to are due to the irritation of the tubercle-bacillus; of most we do not yet know the pathology. But it would in no way count against the view we have taken of scrofula if we had to admit that the alimentary tract of scrofulous children was more liable to, and more easily irritated by, abnormal fermentations than that of healthy children, or that the bronchi of the former were more prone to catarrh. We have already admitted the latter for the hereditarily tubercular, and there can be little doubt that chronic bronchial catarrh renders tubercular infection more easy. This would be a case of grafting a tubercular affection upon a simple chronic inflammation; but to assume that all scrofulous glands, bones, and joints begin as a simple inflammation, and continue simple if they recover, but that they have become tubercular if they take an opposite course, is gratuitous, and not in accordance with the fact that the products of many long-quiescent scrofulous inflammations will excite general tuberculosis if inoculated upon animals.

CHAPTER XXXIII.

LEPROSY.

THIS disease is endemic in many parts of the world, especially in the East and West Indies, China, South America, and Equatorial and Southern Africa. From the fourth to the fourteenth century it was widely spread over Europe, reaching its highest point at the time of the Crusades, when thousands in England, France, Germany, and all around the Mediterranean suffered from the disease and numerous leper-asylums for the isolation of the afflicted were founded. It began to die away at the beginning of the fifteenth century, and was relatively extinct by the end of this century, when, curiously, syphilis appeared or became prominent. Leprosy still lingers at many spots in Europe, particularly in Norway, Sweden, and Iceland.

VARIETIES.—There are two chief varieties of this disease—**tubercular** and **anæsthetic.** In the former the lesions affect chiefly the skin, in the latter the nerves.

In **tubercular** leprosy patches of hyperæmia are followed by thickening of the skin and the formation of nodules, which may reach the size of walnuts. They are almost always situate on parts exposed to the air—face, hands, and feet—and appear sometimes singly, sometimes in groups. They may come out in distinct eruptions, separated by long intervals of time. At first firm and red or brownish, they become soft and paler, but do not, as a rule, ulcerate for long periods unless injured. When ulcers do form, they cause great destruction of features and other parts (*lepra mutilans*). Healing may occur. The tubercles may affect other parts of the body, especially the extensor aspects of limbs and the mucous membranes of the eye, nose, mouth, and larynx.

In **anæsthetic** leprosy nodules—or, more often, diffuse cylindrical or fusiform swellings—form upon nerves, especially the ulnar and external popliteal, surrounding long portions of them, affecting primarily the cutaneous and later the muscular branches. The skin supplied is often painful and hyperæsthetic at first, and then becomes anæsthetic, pale, and wastes, together with the paralyzed muscles. A

bullous eruption (*pemphigus leprosus*) in the area of the affected nerve may be the first sign of the disease: the bullæ may dry, leaving pale insensitive patches, or ulcers may remain. Sooner or later ulcers form upon the anæsthetic parts, leading to extensive destruction and dropping off of fingers, toes, and larger portions of limbs (*lepra mutilans*).

The two forms may run their course separately, but often occur together. The anæsthetic variety occurs chiefly in hot climates. In each form the glands receiving lymph from the diseased parts enlarge—first the superficial ones, then the deeper. Infiltration of viscera—especially the liver, spleen, and testes—may occur. Death results, from exhaustion or some intercurrent disease, after a course of eight to ten years in the tubular form on the average, or about twice as long in the anæsthetic.

HISTOLOGY.—To the naked eye the new growths, wherever situate, have the grayish or yellowish, semi-transparent, uniform appearance common to so many cellular structures. Microscopically, they consist of a granulation-tissue: it is made up of small round cells, like leucocytes, and some very large ones—lepra-cells—of which some are spindle or branched, and is much more enduring than the corresponding tissue in tubercle or syphilis: ultimately it too undergoes degeneration, and is absorbed or breaks down. A few vessels lie among them, and the infiltration begins distinctly around the vessels at the most vascular spots in the skin (about glands). The foci run together and the infiltration becomes diffuse, only appearing on section to be cut up into nodular masses by bands of pre-existing connective tissue. The endothelium of the vessels is said sometimes to multiply, and the interpapillary processes of epithelium and the outermost cells of glands may grow into the infiltration and form a network of epithelial rods, as in lupus. Degeneration occurs just as in lupus, and is perhaps brought about by obliteration of the few vessels present. The appearances are well shown in the accompanying drawing, made from a specimen kindly lent by Dr. Thin (Fig. 105).

ETIOLOGY.—According to modern views, endemicity at once excites suspicion that a disease is infective. Organisms have therefore been searched for in leprosy. Hansen[1] and Neisser[2] separately

[1] "Report to the Med. Soc. of Christiania, 1874," *Bresl. ärtzl. Zeitschr.*, Nos. 20, 21, 1879.

[2] *Virchow's Arch.*, lxxix. p. 31.

described a bacillus as specific to leprosy. It is found constantly in all young, primary lesions (not in those secondary to anæsthesia), chiefly in the lepra-cells (Fig. 104, *b*), but also in others, rarely between cells. In old lesions they become granular from spore-formation. They show an active to-and-fro movement in fresh juices, and when cultivated grow into long jointed filaments (Hansen).

FIG. 105.

Tubercular Leprosy, section through skin: *a*. Showing infiltration with leprosy bacilli. × 6. *b* shows individual bacilli in the cells. × 300. *c*. Individual bacilli, showing spores. × 800.

Thin[1] has shown that as regards size and beaded appearance, B. lepræ (Fig. 104, *c*) is exactly like B. tuberculosis; whilst B. lepræ is stained by Weigert's plan for coloring nuclei, B. tuberculosis is not. Like as they are, they are *not* the same. The leprous organism is constant, no matter where the disease may have been contracted. Thin found bacilli in enormous numbers in the lesions he examined, and gave reasons for believing that spread may occur by both lymph- and blood-vessels; the fungi have occasionally been found free in the blood of patients probably suffering from an acute outbreak of tubercles.

The result of **inoculation-experiments** on the lower animals has been in a few instances to produce a local disease in which the organism grew, but no generalization. Neisser produced tubercles in rabbits by subcutaneous inoculation from leprosy lesions, and Damsch by intraperitoneal inoculation of dogs; Hansen failed with rabbits, and Köbner with an ape; Campana and Thin also failed with pure cultivations on both warm- and cold-blooded animals. The bacilli multiply in the anterior chamber of rabbits, but produce no tubercles.

In the *Brit. Med. Journal* for June 29, 1886, Surgeon Hatch of the Bombay army reports the case of a student who, during a post-mortem on a case of leprosy on June 25, 1885, wounded his left

[1] *Trans. Med.-Chir. Soc.*, 1883.

forefinger and abraded his right hand on the dorsal aspect. On the 28th the left supratrochlear gland was painful and swollen, and on the 29th the axillary glands were affected. On the 30th the ulnar nerve was enlarged, hard, and tender, the swelling being moniliform, shooting pain along it, slight fever and malaise. In July there was severe pain in the small of the back and in the spermatic cord and testes; temperature 99–101°. The right spermatic cord and epididymis became hard, nodular, and tender, but by August it was again normal. The hand-muscles supplied by the ulnar were now atrophied, and there was loss of sensation in the ulnar fingers. Dr. Vandyke Carter now confirmed the diagnosis of leprosy. In 1888 it was announced that a convict who had been offered his choice between death, to which he had been sentenced, and allowing himself to be inoculated with leprosy, and who had chosen the latter, had, some years previously, been inoculated with leprous material and had developed the disease in a well-marked form. We may accordingly say that leprosy is inoculable from man to man, even though the rapid development of symptoms be held to cast doubt upon the former of the two cases. But, though **inoculable**, the disease is not necessarily **contagious**; and upon this point opinions differ much.

From time immemorial leprosy has been looked upon as a contagious disease, and lepers have been rigorously expelled from social communities. A very superficial examination throws doubt upon this, for many lepers live in the closest relations with healthy people without communicating the disease. Many have, however, maintained that the disease is communicable under certain conditions (among which susceptibility perhaps ranks high) which are rarely realized. It seems even more difficult, however, to prove the contagiousness of leprosy than that of phthisis.

Kaposi states[1] that in 1872, Dr. Hawtrey Benson of Dublin recorded the infection of a man who had never left Ireland, from wearing the clothes and using the bed of his brother who had returned from India with leprosy, and had died of it; the symptoms in the case were not given. He knows of no other similar case.

Hillis[2] has recently brought forward evidence in favor of origin by contagion.

Lastly, accounts are given of the introduction of leprosy into

[1] *Loc. cit.*, p. 811.

[2] *Leprosy in British Guiana.*

various places and of its rapid subsequent spread; thus, J. C. White reported in 1882 on various places in North America into which the Chinese had carried the disease; and in the Sandwich Islands there has lately been much talk about the enormous increase of leprosy since 1859, owing to the absence of isolation laws. But the latest report (by Gibson, 1886) is unfavorable to spread by contagion having occurred, and regards the advantages of isolation as illusory. The increase is said to be accounted for by careful registration of cases—like the talked-of increase of lunacy in England. Nevertheless, it certainly cannot be doubted that the introduction of a leper into a community has often been followed by spread of the disease. To quote only one instance: Dr. Zuriaga watched the spread of leprosy in the village of Parcent in Alicante (previously free from the disease) from a leper arriving there from a neighboring town. A friend using the same plates, spoons, and glasses as, and sleeping with, the patient soon developed the disease. Up to 1888, 60 cases had arisen in this small village; 45 had died, and 15 still lived. It appeared clear that friends and relatives who avoided contact with the lepers escaped, whilst the careless were attacked.

We may end by noting that leprosy flourishes in all climates and upon all soils; that poor diet, and salt fish especially, do not appear to be factors in its etiology; and that the disease does not seem to be hereditary—children born of leprous parents in leprous places may acquire the disease, and so may outsiders entering such a place.

CHAPTER XXXIV.

SYPHILIS.

THE lesions occurring in the course of constitutional syphilis also belong to the class of Infective Granulomata. They are inflammatory in their nature, but in their seats, distribution, sequence, and histological characters many of them present certain peculiarities which make them quite characteristic of this disease. The primary syphilitic lesion (usually the *indurated chancre*), the secondary lymphatic gland-enlargement, and the subsequent series of changes in the skin, mucous membranes, and, later, in the nervous system, bones, and internal organs, are all of them the results of inflammatory processes

induced by the syphilitic poison, which, being inoculated at any point, spreads through the whole system. Though not yet certainly recognized, the nodular nature of the lesions demonstrates the particulate nature of the cause, and the multiple foci of disease prove its power of multiplication. Long ago Jonathan Hutchinson (senior) pointed out the analogy between syphilis and the acute general infective diseases ("acute specific fevers"), and it has now taken its place in the classification of disease as a "chronic general infective disease."

THE LESIONS OF SYPHILIS: NAKED-EYE AND MICROSCOPIC CHARACTERS.—I. **Early Lesions.**—Many of these are, anatomically, indistinguishable from simple inflammations of the same parts. The rashes, for example, are due to inflammatory hyperæmia, with more or less infiltration of the superficial layer of the skin, enlargement of the papillæ, and often excessive epithelial multiplication. As a rule, these inflammations end naturally in resolution, but in tissues of feeble resisting power they may ulcerate. The early periosteitis (*nodes*), again, is indistinguishable from a traumatic inflammation, and the syphilitic iritis is diagnosed from the rheumatic only by concomitant circumstances.

II. **Later Lesions.**—Equally characteristic, clinically, with the above are the diffuse subacute and chronic inflammations of organs and parts which end in **fibroid induration.** But, anatomically, these are ordinary productive inflammations. Granulation-tissue forms more or less irregularly throughout the organ. At the same time, if the process is subacute, degeneration and disappearance of some of the more or less widely-separated elements of the part occur. Scar-tissue forms from the granulation-tissue, and as it contracts many more of the proper cells of the part atrophy and disappear. The appearance of the infiltration varies in different cases and in different parts of the same organ, consisting now almost wholly of cells with little intercellular substance, or again of more or fewer cells in a markedly fibroid matrix, or, finally, of dense fibrous tissue. The infiltration may be general, but much more commonly comparatively healthy portions of the organ are found between the fibroid indurations. It is the irregular distribution of these lesions which makes them so characteristic of syphilis.

The capsules of organs are irregularly thickened, and peritoneal coverings are sure to be involved, producing more or less general

adhesion to surrounding parts, as is seen in syphilitic hepatitis, splenitis, or orchitis. In the latter case the coincidence of hydrocele proves during life the affection of the tunica vaginalis. The irregular thickening of the capsule is the most marked feature.

As the fibrous tissue contracts the organ shrinks as a whole, and often becomes of stony hardness; but the irregular distribution of the exudation above noted often causes unequal contraction and puckering of the surface, amounting in some cases to the formation of deep fissures, dividing the organ into lobes. In these cases the diffuse growth has probably been combined with the syphilitic tumor or gumma (to be next described), as not uncommonly happens.

Naked-eye examination of a part—*e. g.* testis—which has undergone these changes shows adhesions between the layers of the tunica vaginalis, which contains fluid where not adherent; marked thickening of the tunica albuginea, and, extending from it into the organ toward the mediastinum, dense bands of fibrous tissue; the natural reddish-brown color of the tubules is replaced by a much paler whitish-yellow tint, in which islands of normal tissue may remain. The consistence of the gland is greatly increased. One or two gummata may also be present.

In relation with bone exudations of this kind often ossify. Under the periosteum they cause thickening of the bone; in the Haversian canals and cancellous spaces, increased density of it. (See "Condensing Osteitis.")

These cell-exudations do not always go on to fibroid induration: they may resolve, and generally do so with marvellous rapidity under the influence of iodide of potassium when they are at all recent. Probably the inflammatory products undergo fatty degeneration previous to absorption.

Localized scars, often causing much puckering of the surface of organs and sending fibrous rays far into the surrounding tissue, may be found, and are usually the remnants of precedent gummata.

Gummata, Syphilitic Tumors, Syphilomata.—Anatomically, these are the characteristic lesions of syphilis; they are frequently associated with the fibroid lesions. As usually met with, they are moderately firm yellowish-white nodules, having often, on section, somewhat the appearance of the cut surface of a horse-chestnut. They vary in size from a hemp-seed to a walnut, and are surrounded by a zone of translucent fibrous-looking tissue, which sometimes has the appearance of a capsule, and which is so intimately associated with

the surrounding structures that enucleation of the mass is impossible. The outline of the growth is generally irregular from processes radiating from it along the natural septa of the organ, and examination always shows that spread occurs by infiltration. In the earlier stages of their development, when they less commonly come under observation, they are much softer in consistence, more vascular, and of a reddish-white color, whilst in their more advanced stages, owing to extensive retrogressive changes, they may be distinctly opaque, yellow, and fatty.

Examined microscopically, gummata, as usually found, show marked structural differences between the central and external portions of the growth. The central portions are composed of closely-packed shrunken cells and nuclei, fat-granules and cholesterin, amongst which is generally a little fibrillated tissue (Fig. 106, *a*). Surrounding this and directly continuous with it is a zone of cells in a distinctly-fibrillated matrix; whilst the peripheral portion of the growth is a richly cellular and vascular tissue (Fig. 106, *b*, and Fig. 107). This peripheral layer, which is in direct histological continuity with the surrounding structures, consists of small cells, many of which resemble white blood-corpuscles, whilst others are larger and like the formative cells of granulation-tissue: giant-cells also are found, but less commonly than in tubercle. These cells are separated by a scanty, homogeneous, intercellular material and numerous new blood-vessels. The three zones already described, which are to be distinguished more or less clearly in most fully-developed gummy nodules, correspond with three different stages in their growth. Fatty degeneration may follow very closely on the spreading edge and render the two outer zones very narrow: although to the naked eye the yellow patch may seem defined, the microscope shows that each one of these zones passes gradually into the next. The most external zone, consisting of the vascular granulation-tissue, represents the earlier stage of development, and by the continuous formation of this tissue the growth may steadily increase. The intermediate more fibrous zone represents the second stage in the process—the development of the granulation-tissue into a more or less com-

FIG. 106.

Gummy Growth from Liver: *a*. Central portions of growth consisting of granular débris. *b*. Peripheral granulation-tissue. *r*. A blood-vessel. × 100. (Cornil and Ranvier.)

pletely fibrillated structure. The characters of this fibrillated tissue vary in different growths. In some the fibrillation is very distinct; in others the tissue is dense and cicatricial in character; whilst less frequently it consists of a reticulated structure within the meshes of which are grouped round small cells. The central zone, consisting of the amorphous granular material, represents the oldest portion of the growth, that which has undergone retrogressive changes. The blood-vessels in the centre of a gumma undergo certain changes, about to be described, by which they become obliterated. The parts are thus deprived of blood, and hence degenerate. This takes place very early. When the tumor is large it may sometimes be seen to be made of several distinct smaller growths, each presenting at its circumference the more perfect cells, whilst the central parts are granular and amorphous.

FIG. 107.

The Peripheral Portion of a Gummy Growth in the Kidney, showing the small-cell granulation growth in the intertubular tissue. × 200.

In early stages, before they have produced marked destruction of tissue, gummata may be absorbed. Later, their central fatty portions are frequently absorbed, leaving a radiating puckered scar; calcification is rare. Not uncommonly, under conditions which are not understood, gummata soften and excite suppuration around them; the abscess bursts and a yellow slough is exposed. This has a very characteristic appearance, like "wet wash-leather"—tough and coherent, very unlike the dead tissue thrown out from the caseous centre of a tubercular focus. Slowly it is thrown off, and a larger or smaller cavity is left, with ragged soft margins. All this is often and well seen in the tongue. Gummata of the skin and mucous membranes are by far the most prone to take this course. These ulcerations must be distinguished from the superficial ulcerations connected with the early rashes.

Gummata are met with in the skin and subcutaneous cellular tissue; in the submucous tissue, especially of the pharynx, soft palate, tongue, and larynx; in muscle, fasciæ, bone; and in the connective tissue of organs, especially of the liver, brain, testicle, and kidney. They occur also, but much less frequently, in the lungs, especially in congenital syphilis, as do also simple localized fibroid indurations. They are generally late, so called tertiary, manifestations, but they may occur at quite an early stage. No hard line can be drawn clinically

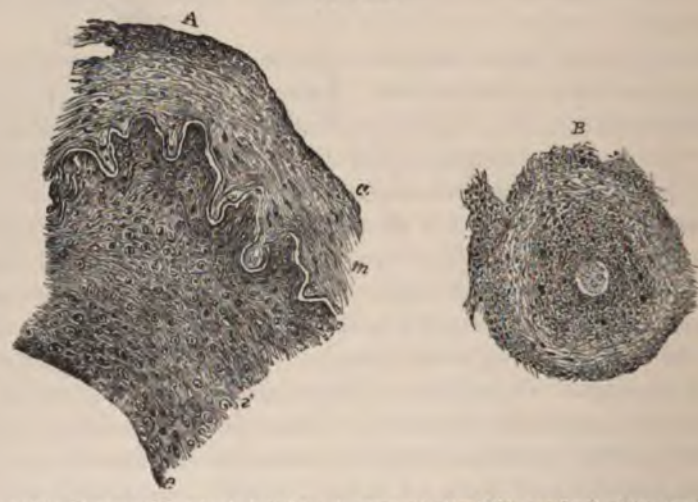
between the secondary and tertiary stages, and none can be drawn pathologically between the products of these stages. All are inflammatory, some circumscribed, some diffuse. Even the hard chancre has the structure of the first stage of a gumma—leucocytes, formative and giant-cells in a fibrillar matrix.

Changes in Vessels.—Certain changes in the cerebral arteries have been described by Heubner as characteristic of syphilis. These changes have been brought prominently before English pathologists by Drs. Greenfield, Barlow, and others.[1]

In the cerebral arteries the changes produce opacity and marked thickening of the vessel, with considerable diminution in its calibre. It is this diminution of the lumen of the vessel which is especially characteristic. The smaller vessels, arteries, and veins are chiefly affected, and their lumina may be quite obliterated.

When transverse sections of the vessels are examined microscopically, the principal change is seen to be situated in the *inner* coat.

FIG. 108.



Syphilitic Disease of Cerebral Arteries: A, segment of middle cerebral artery, transverse section: *i*, thickened inner coat; *e*, endothelium; *f*, membrana fenestrata; *m*, muscular coat; *a*, adventitia. × 200, reduced ½. B, small artery of pia mater, transverse section, showing inner coat, diminished lumen of vessel, and considerable infiltration of adventitia. The cavity of the vessel is occupied by a clot (? thrombus). × 100, reduced ½.

It is well shown in the accompanying drawings made from specimens kindly lent to me by Dr. Barlow (Fig. 108). This coat is consider-

[1] *Trans. Path. Soc. Lond.*, vol. xxviii.

ably thickened by a cellular growth. The growth, which is limited internally by the endothelium of the vessel (Fig. 108, A, *e*) and externally by the membrana fenestrata (Fig. 108, A, *f*), closely resembles ordinary granulation-tissue, consisting of numerous small round and spindle-shaped cells. This tissue appears gradually to undergo partial development into an imperfectly fibrillated structure.

In addition to this change in the intima, the outer coat is abnormally vascular and infiltrated with small cells (Fig. 108, A, *a*), and this cellular infiltration usually invades also the muscular layer (Fig. 108, A, *m*). The marked diminution of the lumen of the vessel (Fig. 108, B) and the consequent interference with the circulation, coupled with change in the endothelium, frequently lead to coagulation of the blood (*thrombosis*) and cerebral softening.

Dr. Greenfield's observations tend to show that similar changes occur in vessels of other parts, and that they account for the degeneration of syphilitic gummata. Aneurism in adults under forty is often connected with a syphilitic history.

ETIOLOGY.—Strong as the clinical evidence of the infective nature of syphilis is, nothing positive is known of its cause. The poison appears certainly to be an organism, probably a bacillus, which enters through a mucous membrane or through an abraded surface of skin, and is carried into the blood indirectly by the lymphatics, and probably directly by the blood also, judging from the failure of early destruction of an infected surface to prevent the general disease. A good many observers have described organisms, but they by no means confirm each other's results.

The poison exists in the primary sore, in mucous tubercles, and all secondary sores, and in the blood during the eruptive period. It is doubtful whether it is present in pure lymph, such as may be obtained from a vaccine-vesicle. It is not present in normal secretions, as saliva, mucus, semen. The discharge from tertiary or gummatous ulcers is not infective.

Klebs described mobile granules and short rods in non-ulcerated primary sores. He inoculated apes with portions of syphilitic tissue, and produced a disease closely resembling syphilis. A cultivation of the blood of such an ape on gelatin yielded brownish masses of short rods, as does also the primary lesion in man.[1] Aufrecht found diplococci staining with fuchsin in the juice of flat condylomata—an

[1] *Arch. f. Exp.-Path.*, x. 3, 4.

observation of no value.[1] Birch-Hirschfeld found diplococci, easily taken for short rods, not only in the papillary bodies and epidermic cells of flat condylomata, but also in gummata of different organs, but only in still-growing specimens, and especially at the edge of the cheesy part. He has since stated that further research proved what he took for diplococci in the liver to be really plasma-cells which stain like organisms with aniline colors: he adheres to his observations on condylomata.[2] Bergmann found organisms resembling those described by Klebs constantly present in the lymphatics of Hunterian chancres.[3] Martineau and Hamonie cultivated in meat-broth similar organisms from the discharge of syphilitic ulcers; the cocci grew into larger chains, and, the authors say, gave syphilis to a young pig.[4]

Lustgarten states that by a special mode of staining he demonstrated in each of some sixteen cases the presence of bacilli very closely resembling those of tubercle and leprosy. They occurred only within the larger cells of the granulation-tissue, and were found in the primary sore, flat condylomata, and gummata. They were slightly curved, their edges showed slight indentations, the ends were sometimes a little swollen, and spores were seen in the interior. They were sometimes single in the cells, sometimes multiple, but as a rule only sparsely distributed.

Other observers have failed by Lustgarten's method to demonstrate organisms in syphilitic lesions, and Alvarez and Tavel have described a similar bacillus as existing in normal smegma preputii.

In a preliminary notice in the *Lancet* (April 10, 1886) F. S. Eve and A. Lingard state that they have succeeded in demonstrating the presence in primary sores, lymphatic glands, condylomata, and gummata of a bacillus in large numbers. The organism is somewhat polymorphous, varying a good deal in length, with rounded, sometimes swollen, ends; usually straight, sometimes curved. The longer bacilli usually stained unequally, and showed 3–5–8 deeply-stained segments united by unstained protoplasm in a hyaline sheath. Unlike the bacillus of smegma (Alvarez and Tavel), this organism after staining with fuchsin is decolorized by nitric or oxalic acid. Lustgarten's method gave uniformly negative results with sections known to be crowded with bacilli.

These bacilli were found chiefly in tissue-interstices and lymph-

[1] *Ctbl. f. med. Wiss.*, p. 228, 1881.
[2] *Lehrbuch d. Path. Anat.*, 2d ed., Part 2, p. 612.
[3] *The Fungus of Syphilis.*
[4] Birch-Hirschfeld, *loc. cit.*, Part 1, p. 187.

spaces, but also in cells. In the hard sore they were much more numerous in the deeper parts than in the granulating surface, perhaps on account of the resistance of granulation-tissue to germs (p. 277). In glands they are most numerous in the cortical lymph-spaces; in condylomata they are found in the tissue-spaces, and in even larger numbers in the epithelium; in gummata they occur chiefly at the spreading margin.

Eve and Lingard succeeded in obtaining cultivations of this bacillus from the blood of two patients in the early eruptive stage of syphilis, and others from the deep surface of an excised papule, from an inguinal gland presumably syphilitic (further history of the patient unknown), and from the base of a hard sore removed by circumcision. An *impure* cultivation was obtained from the base of an excised condyloma, and a pure one from the ichor from a phagedenic sore upon which syphilitic symptoms supervened. No cultivation could be obtained after the administration of mercury for any length of time.

Inoculations of apes with cultivations and with pieces of primary sore and other syphilitic lesions were uniformly unsuccessful.

Syphilitic Disease of the Liver.

The liver is one of the most frequent seats of syphilitic lesions. The most common change is the development of fibroid and gummy growths in the substance of the organ. In the spreading stage the margins of gummata are ill defined, round cells infiltrating the surrounding liver-tissue. The growths—which are usually connected with fibroid thickenings of the capsule—sometimes consist simply of a dense fibroid structure. More commonly, however, gummata are found imbedded in the fibroid growth. In the former case it is possible that the gumma may have become absorbed, leaving merely its fibroid cicatrix.

The development of these growths produces very marked alterations in the form of the liver. Scar-like depressions are seen on its surface, and the organ is irregularly and often very deeply puckered.

A more general fibroid change, not associated with the formation of gummata, is occasionally met with in the liver in inherited syphilis. This change closely resembles ordinary cirrhosis, although the intercellular network of the liver is usually more extensively involved.

Lastly, it must be mentioned that the liver in syphilis is frequently lardaceous.

It is unnecessary to describe particularly syphilitic lesions in other organs, as they all present the same general characters—viz. cell-infiltrations, scars, fibroid indurations, and gummata, singly or combined.

CHAPTER XXXV.

GLANDERS AND FARCY, RHINOSCLEROMA, AND ACTINOMYCOSIS.

GLANDERS AND FARCY.

THESE are varieties of one disease, due probably to difference in the point of entry of the poison. In glanders the nasal mucous membrane and its prolongations are the seat of the earliest lesions; in farcy the skin and subcutaneous tissue. Each form may run a rapid or a slow course, and it is usual in man for the symptoms of one to supervene sooner or later upon those of the other. The diseases are common among equine animals, especially horses, and are communicable from them to other animals, including man. This happens but rarely. It is transferable from man to man.

NATURE OF THE PATHOLOGICAL LESION.—This is best seen in the more chronic forms. It is a circumscribed nodule (**farcy-bud**) varying from a just visible point up to the size of a pea or bean. On section it is found to consist of small round cells: vascularization is very imperfect if it occurs, but the formation of larger cell-forms has not been described. Degeneration occurs early, and more or less acute suppuration is excited. In the substance of an organ or part an abscess forms, but on a free surface an ulcer with indurated, sharply-cut margin and very foul base is the result. Such ulcers may heal, but their course is generally very chronic. In the more acute forms of the disease the poison sets up ordinary suppuration at spots where it develops. The inflammation is not always circumscribed, but sometimes produces diffuse infiltrations, as of muscles, subcutaneous tissue, and connective tissue of orbit, which go on to suppuration at many points or generally. The farcy-buds and diffuse inflammations in the various stages of degeneration, suppuration, and ulceration mentioned above, and in various seats, constitute the morbid anatomy of the disease.

MODE OF ENTRY OF THE POISON.—A wound is a common portal; mucous membranes, especially the conjunctival and nasal, are other seats of infection. In many cases there is no evidence to show how the poison entered.

COURSE.—In acute glanders, after a variable period of incubation, inflammatory nodules appear in the mucous membrane of the nose, frontal sinuses, etc., and run on more or less rapidly to suppuration and ulceration. The submaxillary and cervical glands swell from infection through the lymphatics. The fever and muco-purulent (often bloody) discharge from the nostrils are thus explained. The poison now enters the blood and is carried to distant parts, giving rise to metastatic inflammations in internal organs, especially the lungs, and in the skin and the mucous membranes of the respiratory and alimentary tracts. Abscesses in the subcutaneous and intermuscular tissue are common, and suppuration in joints occurs. In fact, the disease resembles pyæmia in many respects, being, like it, due to the dissemination by the blood of a poison capable of exciting suppuration. The abscesses in organs are generally small, but may reach a large size. The respiratory and alimentary mucous membranes are perhaps directly infected from the nose. On the skin red papules and larger patches of inflammation appear, on which vesicles, and then pustules, often with hemorrhagic contents, quickly develop, constituting the rash of the disease. The earliest stage is a collection of round cells in the superficial part of a papilla; a little later and the rete is raised in the roof of a pustule. Throughout the disease the fever is high, symptoms of prostration appear early, and death occurs with all the signs of septic poisoning.

In **chronic farcy** large "buds" appear in the subcutaneous, submucous, and intermuscular tissue. The former break down slowly and form foul ulcers; the lymphatics become much swollen, hard, and knotted; the glands are greatly enlarged. The general symptoms are much milder. This form often ends in recovery. The symptoms of glanders frequently supervene before death.

ETIOLOGY.—Schülz and Löffler[1] found in the pus of abscesses in glanders slender rods like, but smaller than, B. tuberculosis. Cultivated in the serum of horse's blood, they formed colonies, maintaining their initial form. After repeated cultivation, to ensure purity from

[1] *Mittheilungen aus d. Kaiserl. Gesundheitsamt*, Berlin, vol. ii.

the original pus, different animals were inoculated. The result varied with their susceptibility. In all an indurated ulcer appeared at the site of inoculation, and cordy lymphatics ran thence to swollen glands. In some, metastatic abscesses formed in internal organs; others died early with symptoms of septic poisoning. In all the above bacillus was found. Two horses were inoculated from a fourth cultivation: all the symptoms of glanders set in after some days' incubation, and the older horse died in fourteen days. The other was killed next day, being extremely weak. The post-mortem signs were the same in both—viz. a sore the size of a shilling at the site of inoculation; lymphatics leading thence to glands hard and swollen; abscesses in the lungs from the size of a pea downward, with red borders; the nasal mucosa studded with farcy-buds and ulcers.

By this one series of experiments it would seem that this bacillus has been proved to be the cause of glanders and farcy.

Rhinoscleroma.

NAKED-EYE APPEARANCES.—This disease was described by Von Hebra and Kaposi in 1870; the latter[1] speaks of having seen about forty cases, almost equally distributed between the sexes and occurring in people of all ranks of life between the ages of fifteen and forty. The great majority of the cases came from Vienna or its neighborhood; a few have been recorded in Italy, one or two in Egypt, and some in South America, where, it is said, the disease is not uncommon. The only case recorded in England occurred in the person of a Guatemalan under the care of Semon and Payne.[2] There has been no reason for suspecting any connection with tubercle, syphilis, or other widespreading disease: antisyphilitic treatment has always been without effect.

DISTRIBUTION.—The disease consists in the formation of flat or elevated, sharply-defined plaques or masses of new growth, which are tender, very hard, and elastic, and almost always primarily situate in the skin or mucous membrane near the anterior nares, which they ultimately close, first, however, forcing the alæ apart and rendering them so rigid that pressure makes little impression upon them, and the nose below the bones has been compared to ivory or plaster of Paris; thence they spread on to the upper lip and even around the

[1] *Hautkrankeiten*, 3d ed., p. 752.

[2] *Trans. Path. Soc.*, 1885, p. 73, figs.

whole mouth—greatly narrowing the orifice—and on to the gums, or, more commonly, back through the nasal cavities (both sides being soon affected), blocking the lachrymal ducts, to the hard and soft palates, which become infiltrated, and the latter is greatly disfigured by scar-contraction. The infiltration may spread to the pharynx and glottis, inducing rigidity and closure of the latter orifice, and consequent aphonia and dyspnœa. Involvement of one cheek to such an extent that the nose seemed by comparison depressed, together with a swelling over the parietal, has once been noted (Kaposi); in another case (Pick) both external auditory canals were affected, and the external auditory meatus in a third (Kaposi). The growth has never been known to generalize, and for years the general health is not affected. Extension is slow but steady when there is no treatment, and recurrence has invariably and rapidly occurred after even apparently complete removal.

The masses round the nostril are like keloid or hypertrophic scars, light or dark brownish-red in color, smooth, and fissured here and there. The skin around is quite normal. There is little or no tendency to ulceration—after years it may just be excoriated. Injuries excite little or no reaction: after removal of a piece it grows again and skins over.

HISTOLOGY.—Dense infiltration of the corium with small round cells is found. The cells lie in a stroma which is frequently fibrillated, and usually presents some dense bands, upon which Payne supposes the great hardness of the growth to depend; in some cases, however, cartilage (upper lip, Kaposi) and bone (Billroth) have been found in the stroma. Many of the cells are found to be spindle-shaped, and a few may be "epithelioid," but large cell-forms are the exception. The growth is tolerably vascular and presents no tendency to fatty degeneration. Cornil describes some of the cells as containing "hyaline masses," which may be present also in the tissue: they were noted in the latter situation only by Payne.[1]

As in lupus, down-growth of epithelial processes into the granulation-tissue of the corium is usual.

THE VIRUS.—The question of contagion has not been raised, but the disease is regarded by most authorities as an infective granuloma on account of its morbid anatomy, coupled with the constant presence

[1] *Loc. cit.*

of a bacillus (Frisch), said by different observers to occur in the cells, lymphatics, or tissues. Payne figures them in all three situations. The bacilli are short and thick, ovoid, or even round, and two are often bound together as diplococci in a capsule. Frisch and Barduzzi and Paltauf and Von Eiselsberg have cultivated the organism: it grows rapidly at 36°–38° C. Inoculations with the culture or with pieces of the growth upon the noses of dogs have always failed. Proof of the etiological relation between this germ and the disease is therefore defective.

Actinomycosis.

DISTRIBUTION.—Sarcoma-like tumors, occuring chiefly in the lower jaws of cows, were shown by Bollinger[1] in 1877 to contain constantly elements of a fungus, the **actinomyces**; and he found the same fungus in nodular masses in the tongues of cows (*woody tongue*), in the swollen glands beneath the jaw, and in the upper part of the neck, in polypoid and submucous tumors of the larynx, and throughout the alimentary tract. They have since been demonstrated in tumors of pigs' jaws and udders, and in tubercle-like nodules in the lungs of calves. Horses also may suffer, but the disease is rare in them and in pigs. Carnivora are exempt.

In 1878, Israel described a case of multiple superficial abscesses, with one large intrathoracic abscess opening by fistulæ on the surface. The pus from all contained parasites, which corresponded to the above description. The disease had begun six months before with fever and joint-pains. Three weeks after admission the woman died: there were a great abscess in the left lung and countless abscesses in the liver, spleen, intestine, and kidneys, most of them very small, but some the size of an apple. All contained the fungi, and in the glomeruli of the kidney were found fungi which had not yet excited inflammation. Since 1878 at least forty cases have been recorded, thirty-eight of them being collated in Israel's work on *Actinomycosis in Man*, abstracted in the New Sydenham Society's *Micro-parasites in Disease*.

HISTOLOGY.—On section these nodules have a spongy, open appearance, and a puriform or cheesy fluid can be squeezed from them. Besides fatty cells, this contains many pale-yellow granules as large as millet-seeds. These, when gently squeezed and cleared up by potash, are seen to consist of filaments radiating from a common

[1] "Ueber eine neue Pilz-krankheit beim Rinde," *Ctbl. f. d. med. Wiss.*, 1877, No. 27.

centre, and bearing at their free ends club-shaped swellings, often branched and frequently calcified. The nodules and tumors consist largely of granulation-tissue, intersected here and there by bands of fibrous tissue. In the older specimens there are found round each fungus giant-cells, and outside these epithelioid and then granulation-cells—all signs of a chronic inflammation round a slight, constant irritant.

MODES OF ENTRY OF THE VIRUS.—Israel states that the fungus may enter in three ways:

1. **From the Mouth,** usually through a carious tooth, sometimes through an extraction-wound: by one of these channels it reaches the interior of the jaw (usually lower), and grows there, bursts through the outer plate, and gives rise to an abscess in the glands or connective tissue of the neck. It is probable that infection may take place through the follicles of the tonsil in tonsillitis or of the pharynx in pharyngitis (*prevertebral abscess*).

2. **From the Respiratory Passages.**—In one case a chronic bronchitis (seven years) only seemed to be present; the sputum was then copious and contained the actinomyces. Usually the fungus is drawn into the fine bronchi and alveoli, and there sets up a broncho-pneumonia. The patches enlarge, undergo fatty degeneration and softening, being meanwhile shut off from the healthy lung by a layer of healthy granulations which develops into dense fibrous tissue. The cavities run together, the symptoms being very like those of phthisis, though marked hæmoptysis is uncommon. Then, adhesions over the diseased area having formed, the fungus spreads to the posterior mediastinum, through the diaphragm into the peritoneum (causing *peritonitis*), liver or spleen (*abscess*), or into the anterior mediastinum and pericardium. Lastly, some of these abscesses after much burrowing find their way to the surface and burst. It is noteworthy that though the actinomyces affects the lung from above downward, like the tubercle-bacillus, it leaves the apex, above the clavicle, uninvolved.

3. **From the Intestine.**—The intestine may be affected primarily from within, or, secondarily, by embolism or by extension from other organs. The primary form may lead merely to catarrh, or to the development of foci in the submucous tissue or mucosa, which break down into ulcers with undermined edges reaching down to the muscularis. Perforation into the peritoneum, into other hollow viscera, or through the abdominal wall may result.

In a good many cases the channel of infection remains doubtful.

EXTENSION OF THE DISEASE.—Actinomycotic embolism may lead to abscesses accompanied by symptoms of pyæmia: secondary growths have been seen in all organs and in distant parts; and Ponfick has seen a granulation-mass growing into the jugular in a case in which there were growths in the right auricle and ventricle.

The **NATURE OF THE PARASITE (ray-fungus)** found in actinomycosis, and its botanical position, are not determined. It is believed by many to be the conidia-form of perhaps some known species. Some think that it is a form of leptothrix.

SOURCES OF INFECTION.—Israel thinks that in some of his cases he has been able to eliminate the possibility of infection by means of diseased beef or pork, and that the germ must have entered with water or vegetables: water is unlikely as a nidus, for it soon destroys the adult fungus, but Jensen has traced an epidemic of actinomycosis in Iceland to eating rye grown on soil recently reclaimed from the sea.

CHAPTER XXXVI.

INFLAMMATION OF SPECIAL TISSUES AND ORGANS.

THERE is nothing more to state concerning the process of inflammation, wherever it may occur. Every tissue in the body may be inflamed, but whilst this is common in some, it is rare in others. Certain forms of inflammation occur with especial frequency in certain parts, and the same part may present different appearances under the same form of inflammation. To these and similar points attention must now be directed.

The student should have quite ready in his mind the different forms of inflammation, and their names should bring before him a picture of the tissues infiltrated by a certain exudation: the possible fates of each exudation—complete absorption, imperfect absorption and its consequences, or death—must also be felt instinctively.

INFLAMMATION OF THE CONNECTIVE TISSUES.

Common connective tissue accompanies blood-vessels everywhere. When vessels are injured this tissue is more likely than any other to share in that injury, and if the vessels alone are damaged it will be the first structure to experience the effects of the lesion. Thus, every form of inflammation occurs in connective tissue; the whole description of the process applies to it.

With regard to the special varieties of connective tissue, we shall speak first of the **non-vascular—cornea** and **cartilage,** both of which are interesting as the battle-grounds upon which the origin of the new cells in inflammation have been fought out, for it was hoped that migration from vessels would here be done away with. But we already know from Senftleben's experiments (p. 249) that injury of the cornea produces none of the anatomical signs of inflammation unless the marginal vessels are affected or leucocytes are admitted from the conjunctival sac. About the third day, however, after destruction of cells regenerative processes set in. Observations on cartilage are more difficult, but they show that the above results hold good.

Inflammation of the Cornea.

Anteriorly and posteriorly, the cornea is limited by membranes sufficiently stout to resist the passage of leucocytes, but these enter freely from the margin, together, doubtless, with fluid exudation from the vessels, along the lymph-channels in which the cells and nerves lie, the leucocytes accumulating in clusters around the cells. Such exudation is accompanied by softening and opacity of the corneal structure, and may lead to alteration in its curvature. This happens in vascular keratitis and the interstitial inflammation of congenital syphilis. A slight vascular exudation forms beneath the roughened epithelium as a consequence of the irritation of granular lids, the condition being known as *pannus;* pus may form between the layers of the cornea, constituting *onyx;* and ulcers in all stages are common. They heal by scar-tissue, and leave an opacity and a more or less altered corneal curve. Any keratitis may be "productive," and result in opacity and altered curve.

Inflammation of Cartilage.

In the most acute inflammations of joints the cartilage may slough

bodily, as the cornea does in the worst cases of conjunctivitis, from injury and lack of food combined. It then either peels off in flakes or softens and wears away at points of pressure. In less acute cases

Fig. 109.

× 55

Edge of Cartilage of Knee in Tubercular Arthritis, resting upon inflamed bone, a[redacted] markedly eroded on this aspect, overgrown by a synovial fold (soft) of the free surface; s[redacted] eral channels, along which cell-processes have pushed their way to the capsules of cartila[redacted] cells, have been laid open. (From a specimen of Mr. F. T. Paul.)

it may be invaded by leucocytes from the joint-cavity or from t[redacted]he bone. In the former case some white corpuscles may penetrate t[redacted]he

Fig. 110.

Section of Inflamed Cartilage: *a*. The normal cartilage-cells. *b*. The same enlarged. [redacted] Multiplication of cells within their capsules. *e*. Eroding layer of granulation-tissue. × [redacted] (Cornil and Ranvier.) Many of the cells are probably invading leucocytes.

injured part from the synovia; but the usual course is that the sy[redacted]vial membrane becomes thickened by a vascular round-celled infil[redacted]tion and sends processes inward over the surface of the cartila[redacted]; these creep on, adhering like ivy, and their cells penetrate into [redacted]he

substance of the cartilage, eroding it. Primarily or secondarily to this process, the subjacent bone may inflame, and granulation-tissue springing from it may similarly eat its way through the cartilages at several points, riddling it; or it may spread out beneath its cartilage without perforating it, but loosening it so that it may fall into the joint-cavity. As a rule, no sign of multiplication of cartilage-cells is seen, although leucocytes naturally collect in their capsules (Fig. 109); but in rheumatoid arthritis, if the disease is inflammatory, multiplication of the cartilage-cells until the distended capsules burst into the cavity of the joint is the characteristic lesion. Regenerative changes probably occur in chronic cases. In such a joint the fluid is always turbid from degenerating leucocytes and their products, thus differing from that of serous synovitis; the transition to pus is easy, with more intense and otherwise suitable (p. 281) irritation. Healing takes place by the formation of scar-tissue from the round-celled exudation; short, extremely strong, and wide adhesions often bind the surfaces together, producing *fibrous ankylosis*. If the bone is involved some or all of the adhesions will ossify—*bony ankylosis*.

Inflammation of Bone.

Inflammation of bone always originates in its vascular structures—the periosteum and medulla. **Periosteitis** implies that the periosteum is inflamed, but the superficial layers of the bone always suffer too. It is usual to speak of an **osteitis** when the medulla lying in Haversian canals or cancellous spaces is chiefly affected—of a **myelitis** when the medulla in the canal of a long bone is most markedly involved. Strict limitation of inflammation to one of these parts does not occur; hence such a term as *osteomyelitis*.

Periosteitis.—A **serous** form is described. It is rare, and is the mildest form of infective inflammation of the part. The exudation is highly albuminous (ostéite albumeneuse, Ollier).

Fibrinous and **productive** inflammations are common as the result of injury and syphilis. The early syphilitic node consists of granulation-tissue which may be absorbed or go on to the production of fibrous tissue, which may ossify. It very rarely breaks down. Ossification begins beneath the periosteum and from the surface of the bone. The vessels entering the Haversian canals in the latter are, on account of the elevation of the periosteum, more or less ver-

tical to the surface; hence the new Haversian canals have the same direction. At first well defined and easily separable from the old, the new and the old ultimately become indistinguishably blended. Later in syphilis, when gummata form beneath the periosteum, it is common for suppuration and superficial caries to occur. The subcutaneous bones are chiefly affected. Inflammatory thickening of a bone is always due to periosteitis.

Suppurative periosteitis is generally a part of the infective disease known as **acute necrosis,** which rarely, if ever, occurs after union of the epiphysis. It is believed by some that the poison lodges in the medulla, excites suppuration here, and spreads through the Haversian canals to the periosteum to set up the same process; but probably it may affect the periosteum primarily and alone. Pus forming beneath this membrane strips it up over a larger or smaller area; the vessels passing into the bone are greatly stretched, and this, together with the primary damage to the vessels, induces thrombosis of many. Hence superficial necrosis is the usual result; and if the medulla also has suppurated the necrosis will be *total*—involve the whole thickness of the shaft. Pyæmia commonly occurs before the abscess is opened; it is in this disease that infective fat-embolism probably occurs. In **septic osteomyelitis** a diffuse suppurative inflammation attacks the medulla and periosteum, causing total necrosis of large portions of bone, and very frequently destroying the patient by pyæmia.

OSTEITIS.—The mildest form described is that in which granulation-tissue is produced. This occurs much oftener in cancellous (vertebræ, tarsus, carpus, epiphyses of long bones) than in compact bone. A round-celled infiltration takes place in the medulla and presses into the Haversian canals; the fat-cells disappear before it, so also does the hard substance of the bone; cancellous plates are eaten through and Haversian canals widen. A section shows the spaces crowded with small round cells, often developing in parts into fibrous tissue, and on the surface of the bone, in contact with them, are seen semilunar erosions, as if small bites had been taken out of it. These are called Howship's lacunæ. Each contains leucocytes, formative cells, and often a giant-cell. These cells are eating away the bone. The normal bone-corpuscles remain unchanged so long as they are distinguishable. This process is called **rarefying osteitis,** and is an ulceration or **caries** of bone without formation of pus (*caries*

sicca). Nothing is more natural than that a bone thus weakened should yield to pressure; thus bodies of vertebræ may disappear more or less completely, those above and below becoming approximated; and shafts of long bone bend markedly, as is seen in *osteitis deformans* (Paget) and other diffuse inflammations. The inflammatory tissue may pursue any of the courses mentioned at p. 259 *et seq.*

In a very early case absorption might occur and regeneration make good any loss. But when once marked destruction of bone has occurred, scar-tissue must form and ossify if a cure is to be effected; and this is what happens in cases of spinal curvature without abscess. Too often, however, degeneration and softening of the cells, with more or less "suppuration," occur, a **cold abscess** resulting (p. 307). When this is opened the ulcerating **carious** surface of bone is exposed. If healing occur, it is by the development of healthy granulation-tissue and subsequent scar-tissue, which ossifies. Tubercles are almost always found in such carious processes. Syphilis is another cause.

Death and breaking down of the infiltrating granulation-tissue leads to death of the infiltrated bone; the pieces which come away are generally of small size—**caries necrotica.**

In the most chronic forms of osteitis no rarefaction of bone occurs; the new growth slowly ossifies and the Haversian canals and cancellous spaces diminish. The bone consequently becomes extremely heavy and ivory-like; it is generally thickened irregularly from coincident periosteitis. This occurs, especially in the long bones and in the bones of the skull, from syphilis. It is called **condensing osteitis** or **sclerosis.** It is said that simple closure of a large number of Haversian canals may lead to death of the affected bone. In syphilitic necrosis of the skull the sequestrum is often very dense; it has probably been killed by degeneration and death of the inflammatory products in the bone around the sclerosed patch, and consequent destruction of the few vessels which enter it.

Nothing is commoner than to find rarefying and condensing osteitis combined. Around carious patches osteoplastic periosteitis and condensing osteitis frequently exist, thickening and rendering more dense the surrounding bone. It may be that this less acute inflammatory process is coupled with true hyperplasia of the bony tissue.

NECROSIS.—We have already seen that death of bone may result

in several ways from different forms of inflammation, each leading, however, to destruction of vessels and arrest of nutrition.

This may be brought about by injury stripping off the periosteum and breaking up the medulla; but the extreme rarity of necrosis, even in the most serious simple fracture, shows that injury alone, with such inflammation as it excites, is scarcely to be regarded as a cause. It may act indirectly, however, by preparing the nidus for septic (in compound fractures) and infective organisms. These constantly-acting and severe irritants increase the damage so much that more or less extensive thrombosis, with death of the parts, ensues.

Suppuration beneath the periosteum and in the medulla are *the* causes of necrosis. This result is much commoner in compact than in cancellous tissue, owing to the greater ease with which exudations compress the vessels in the unyielding channels of the former. Necrosis may occur also in a less violent way in rarefying and condensing osteitis (see *antea*), by death of the infiltration.

The piece of dead bone is called a **sequestrum**; it is cast off by a process of caries described on p. 42. It may be **total**, involving the whole thickness; **superficial** or **central**—the latter being much the rarer.

The removal of the sequestrum is often effected only with considerable difficulty, especially if it be deeply seated. This difficulty is occasionally (*in central necrosis*) due to a more or less thick layer of the old bone surrounding the necrosed portion. Much more frequently, however, it is owing to the participation of the periosteum in the inflammatory process. The inflamed periosteum produces new bone, a capsule of which is thus formed, enclosing the sequestrum. Openings (*cloacæ*) exist in this capsule leading to the dead bone, and through these openings the inflammatory products are discharged. When the sequestrum is quite superficial its removal is of course more readily effected.

There are two other morbid conditions of bone, which, although probably not coming within the category of inflammation, may conveniently described in the present chapter—viz. **Mollities Ossium** and **Rickets**.

MOLLITIES OSSIUM.—Mollities ossium or osteomalacia is a rare disease, occurring only in adults, and especially in pregnant women who have borne many children. It is characterized by pro-

gressive decalcification of the bones, whilst the marrow increases steadily and becomes converted into a vascular round-celled structure. All bone is gradually absorbed, except a thin layer beneath the periosteum, so the bones become mere shells in extreme cases, very light, easily cut with a knife, bending or breaking readily. Early in the disease fractures unite. On section in early stages the cancelli and Haversian canals are enlarged and full of a reddish, gelatinous substance, which at a later period may become yellow and fatty.

The nature of the disease is obscure. Sporadic cases occur everywhere, but it is frequent in some places, as in certain valleys about the Rhine, where, it is stated, there are women living who have undergone Cæsarean section for deformed pelvis more than once. The pelvic deformity is of chief importance, the sacrum is pushed downward by the weight of the body, and the acetabula upward and inward by the resistance of the femora, thus greatly shortening the two oblique diameters.

Lactic acid has been found in the bone, the reaction of which is said to be acid, and in the urine. The latter usually contains excess of lime salts which have been removed from the bone and eliminated.

RICKETS.—This disease of children is so specially frequent in the large towns of England that it has acquired on the Continent the name of the "English disease." It appears to be caused by defective hygienic conditions, especially bad air and improper feeding. It is particularly common in children brought up by hand, and, according to Sir W. Jenner, becomes more severe in the *later* children of poor families. It may probably be said that all conditions which materially interfere with the nutrition of a child may cause rickets, and among these the absence of *fresh* food ranks highest.

The disease is characterized mainly by changes affecting the growing tissues of bones, and therefore most marked where growth is most active—viz. at the epiphyses of long, and at the margins of flat, bones. These changes produce undue softness and consequent bending or breaking (green-stick fracture). The bone-lesions are accompanied by symptoms of general ill-health, and often by enlargement of the liver, spleen, and, less often, of the kidneys and lymphatic glands, due chiefly to increase of their interstitial connective tissue, but in part also to overgrowth of their essential structure (Dickinson).

The alteration in the bones may be briefly described as consisting in "an increased preparation for ossification, but an incomplete per-

formance of the process" (Jenner). If we look at a section of the end of a healthy, growing long bone we see the white epiphyseal cartilage adherent along a straight line to the shaft, which consists here of loose cancellous tissue, the spaces of which are filled with red marrow. Between the bone and the epiphysis is a blue, semi-translucent band about one millimeter broad with practically straight margins. Microscopically, the blue line is found to consist of the one or two layers of cartilage-cells which normally multiply and enlarge, forming the well-known oval groups among which ossification proceeds. The septa between the groups have become very thin, and toward the shaft they are calcifying: a sudden transition from the cartilage-cells to those of the vascular red marrow is seen. So soon as these spaces (*primary areolæ*) with calcified walls are occupied by the round-celled marrow, absorption begins, and adjacent spaces open into each other and form the larger *secondary areolæ*. On the walls of these laminæ of bone are deposited, including osteoblasts in lacunæ between them, and thus Haversian systems are gradually developed. The calcified cartilage-matrix is darker and more granular than the bone laid down by the medulla which gradually replaces it.

In a rickety bone the blue transition-zone is in its elements like that in health, but is much wider than normal, affecting several rows of cells, and its outlines toward the bone and toward the cartilage are very irregular, the calcification of the matrix to form primary areolæ occurs without any regularity, so that patches of calcification or of young bone may be found in the transition-zone detached from the shaft, and oval collections of cartilage-cells are seen among secondary areolæ full of red marrow. Speedy fusion of the primary into secondary areolæ occurs, but the deposit of laminæ of bone is insignificant.

Beneath the periosteum osteoblasts form in excess of the normal and osteogenic fibres appear, but calcification is very backward. Central absorption goes on as usual to form the medullary cavity, and the sound bone which was laid down before the onset of the disease, and which was distinguished from the rickety bone by its greater density and less opaque aspect, is gradually removed. The bone, now consisting only of the soft rickety structure, yields more or less readily under pressure or breaks under slight violence. The fracture, however, is often incomplete. When bending occurs, Nature endeavors to support the concave side by throwing out along it a buttress of bone. This is often seen in the femur and tibia, giving the bones a flat, somewhat razor-like appearance.

The thickening of the epiphyses, the displacements which occur about the junction of shaft with epiphysis, the thickenings of the edges of the cranial bones (*e. g.* the parietals), and the abnormal curvatures of bones under pressure, are readily explained by conditions such as the above.

The process above described seems to be injurious to the subsequent growth of the epiphyses. They often join the shafts early, dwarfed stature being the result.

FIG. 111.

Section of Rickety Radius, showing excessive multiplication of cartilage-cells and their arrangement in rows, and slight ossification of osteogenic fibres extending irregularly into the cartilage. (Dr. Mott.)

We may just mention on account of its importance the **rickety pelvis.** There are two forms. The first shows shortening of the conjugate diameter only, and is contracted in cases in which the child, being unable to walk, is kept lying. The other closely resembles the osteomalacic pelvis, and the mechanism of its production is the same, for it occurs in children who are able to walk about.

CHAPTER XXXVII.

INFLAMMATION OF BLOOD-VESSELS.

Inflammation of Arteries.

It is generally taught that the middle and inner coats of arteries are non-vascular, the *vasa vasorum* not penetrating beyond the external coat; also, that the intima is nourished from the blood in the vessel. But Dr. F. W. Mott has shown that in normal arteries the *vasa vasorum* do enter the *media*, and he makes the very probable suggestion that the *membrana fenestrata* is fenestrated to allow fluids to pass from these vessels into the *intima*. In support of the view that the intima, apart from the endothelium, is not nourished from the

Fig. 112.

Section of a Thrombosed Popliteal Artery a fortnight after ligature, showing persistence of almost the whole of the intima. The thrombus has been torn from the vessel-wall. (By Dr. Mott.)

main stream, Dr. Mott shows it persisting around thrombi which must have cut off this source of supply (Fig. 112). As to the endothelium, *if it be true* that it multiplies and sends rod-like anastomosing proc-

esses of cells into organizing thrombi, surely it cannot be wholly dependent upon the main blood-stream for its nutriment.

As in other tissues, inflammation of arteries may be acute or chronic.

ACUTE ARTERITIS.—Acute idiopathic arteritis was formerly regarded as common, the staining of the inner coat which occurs in septic fevers being mistaken for inflammatory hyperæmia. No such disease is now recognized. Acute inflammation may be produced by **injury**, as when a vessel is tied, twisted, etc., or damaged by the formation or impaction in the vessel of an irritant body (**thrombus** or **embolus**), or by **extension** from surrounding parts. The changes in traumatic arteritis are described at p. 219, and the effects produced by a simple thrombus are similar. Plugging of an artery by a simple embolus causes only a chronic inflammation, but the infective emboli in cases of ulcerative endocarditis, etc. are believed to produce acute infiltration and softening, and to be the chief cause of aneurism in young people. In arteritis by extension the outer coat is first and chiefly affected; if the process extends so as to affect the intima, the endothelium becomes shed and thrombosis results. Thus destruction of vessels by ulceration does not cause hemorrhage unless the clot breaks down, as it possibly will if infected from a foul wound: this *septic arteritis* is the commonest cause of secondary hemorrhage.

CHRONIC ENDARTERITIS.—Whilst the acute inflammations affect more or less generally the whole thickness of the artery, the chronic inflammations affect primarily and perhaps solely the deeper layers of the intima. Hence the term **chronic endarteritis.**

The causes of chronic endarteritis are **mechanical strain** and **syphilis.** The former has been shown by Moxon to be the cause of those very common changes in the larger arteries after middle life which go by the names **chronic endarteritis, arteritis deformans,** or **atheroma.** The proofs adduced are—the much greater frequency of these changes in the aortic than in the pulmonary system; their occurrence in the latter when the pressure is raised, as in mitral obstruction; their relative frequency in those systemic arteries which are most exposed to strain, especially the arch of the aorta; and the effect of conditions which raise the blood-pressure in producing them. Thus, athletes are very liable to the disease, and chronic Bright's disease, in which the high-tension pulse is well known, is a common

cause of atheroma. **Syphilis** as a cause of endarteritis has been considered in a preceding chapter (see p. 346).

Atheroma affects chiefly the larger vessels of the trunk and limbs and those at the base of the brain. It commonly forms rings round the mouths of branches leaving a main trunk. It appears as slightly prominent yellowish patches covered by normal endothelium; in fact, this and the superficial layers of the intima may be stripped off, leav-

FIG. 113.

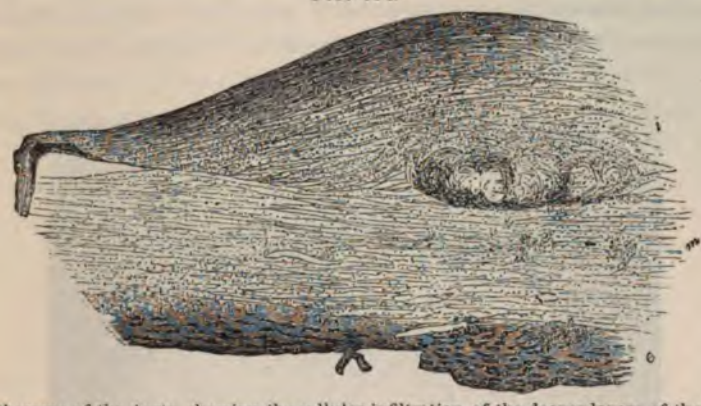
Section of an Aorta (external coat) in an Early Stage of Arteritis, showing periarteritis and cell-infiltration from the vasa vasorum. It was a markedly syphilitic case. (Section and photo by Dr. F. W. Mott.)

ing the diseased tissue beneath. It thus contrasts strongly with the superficial fatty patches which result from fatty degeneration of the endothelial and subendothelial connective-tissue cells (p. 69).

In the earliest stage of the process a grayish, semi-translucent, round-celled infiltration is found between the laminæ forming the deeper part of the intima. This may go on to the production of fibrous tissue, a dense fibroid plaque or more diffuse thickening resulting; more often formation of fibroid tissue and fatty degeneration are found together (Fig. 114), or fatty degeneration and calcification may occur, or the fatty degeneration may lead to complete softening. Then a soft, yellowish, pultaceous material, consisting of fatty débris and cholesterin crystals, is found beneath the intima. This has been

termed an **atheromatous abscess.** If the lining membrane perishes or is torn, the softened matters are carried away by the blood-stream,

FIG. 114.



Atheroma of the Aorta, showing the cellular infiltration of the deeper layers of the inner coat, and the consequent bulging inward of the vessel. The new tissue has undergone more or less fatty degeneration. There is also some cellular infiltration of the middle coat. *i.* Internal, *m.* middle, *e.* external coat of vessel. × 50, reduced ½.

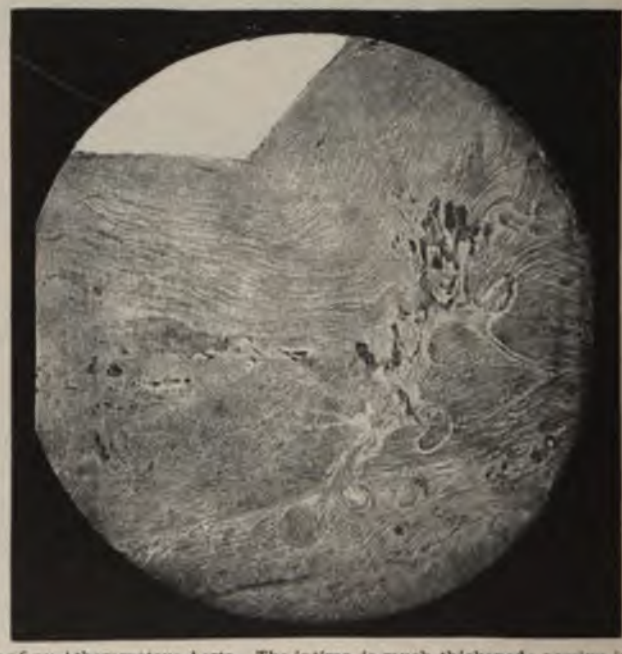
leaving an **atheromatous ulcer.** The middle and external coats become more or less infiltrated with leucocytes and converted into fibrous tissue.

It is not uncommon to find the arch of the aorta so studded with small, thickly-set, raised plaques that it looks somewhat like alligator-hide. The plaques are yellow, many of them perhaps calcified, and the calcareous plates may be quite bare or covered by endothelium or a little fibrin; atheromatous abscesses and ulcers may also be present. The orifices of the coronary arteries are often more or less diminished by yellow rings around them, and the blood-supply to the heart proportionately lessened.

The cause of the fatty metamorphosis of the round-celled infiltration has been variously stated. Köster and Kraft believe that a **mesarteritis** or infiltration of the media is the primary change in atheroma, and that conversion of the cell-infiltration into fibroid tissue causes constriction of the vasa vasorum which send fine branches into the inflammatory patch in the intima; consequently this degenerates. But Orth and most authors deny that a mesarteritis either precedes or even accompanies the infiltration of the intima. Mott believes that fatty changes in the latter result from an endarteritis of the vasa vasorum, leading to a progressive narrowing of their lumina: this is illustrated in Fig. 115.

It is obvious that atheromatous changes will greatly impair the
ticity of a vessel and render imperfect the circulation in the
beyond. Moreover, the *inelastic* vessel-wall tends slowly to
under the *constant* pressure to which it is subject. General dilat
of the vessel results, perhaps even a **fusiform** or **cylindriform an**
ism. When an atheromatous ulcer forms the vessel is specially w
ened at this spot, and a **sacculated aneurism,** or even rupture,
occur if the external coats have not been greatly strengthened b

FIG. 115.



Section of an Atheromatous Aorta. The intima is much thickened; passing in fr
externa through the media are vessels, about which hemorrhage (black shadin
occurred; the lumina of the main trunks of these in the externa are almost obliter
an endarteritis. (Specimen and photo by Dr. F. W. Mott.)

formation of inflammatory tissue in them. And if, when an ab
bursts, the tissues round its margin have not been matted togeth
the new tissue, the blood may find its way into the substan
the middle coat, between the internal and external, forming a
secting aneurism. This occurs only in the aorta and its l
branches. Ultimately the blood may burst through the externa
or through the internal into the interior of the vessel.

Inflammation of Veins.

Inflammatory processes in veins are more frequent than in arteries, but here they are in the very great majority of cases **secondary** to coagulation of the blood within the vein (**thrombosis**), the coagulum

Fig. 116.

Section across a Portal Canal in a Case of Suppurative Pyle-phlebitis arising in Connection with "Umbilical Pyæmia." The vein-wall is converted into granulation-tissue. (Lumen of vein below on left.)

exercising an injurious influence upon the coats of the vessel. These inflammations resulting from thrombosis have already been described (p. 223). They are localized or spreading, according as the clot is simple or continued (p. 218).

Other **causes** of phlebitis are violent **injury** and **extension** of inflammation from adjacent tissues. Paget describes a gouty phlebitis especially common in the internal saphenous, and often recurrent.

The structural changes closely resemble those in the arteries. In phlebitis from injury or from extension the external and middle coats become infiltrated with cells, the vitality of the intima ultimately becomes impaired or lost, and when this has occurred the blood with-

in the vein coagulates. In phlebitis from thrombosis the intima must suffer earliest.

Less commonly than in arteries we find the veins, especially in the lower limb, studded internally with irregular calcified plaques.

When a clot undergoes infective puriform softening (Fig. 116), the vein-wall becomes densely infiltrated with cells and presents much the same appearance as when it becomes infiltrated by extension from a foul wound (**acute septic phlebitis**).

CHAPTER XXXVIII.

INFLAMMATION OF THE HEART.

INFLAMMATORY processes in the heart may affect the substance of the organ or the endocardium. They are much more frequent in the last-named situation.

ENDOCARDITIS.

Endocarditis is for the most part limited to the valves of the heart, although it is occasionally met with involving more or less of the cardiac cavities. After birth the process is almost exclusively confined to the left side of the organ, and in the great majority of cases

FIG. 117.

FIG. 118.

FIG. 117. Inflammation of the Aortic Valves. The earlier stage of the process, showing the situation of the inflammatory granulations.

FIG. 118. Inflammation of Mitral Valve. The earlier stage of process. Valve seen from the auricular surface, showing the situation of the inflammatory granulations.

it commences in, and comparatively rarely extends beyond, the confines of the aortic and mitral valves and corresponding orifices. But

during fœtal life endocarditis is as exclusively confined to the right side (arterial), giving rise to congenital valve-lesions. It is those portions of the valves which come into contact in the act of closure, and are thus *most exposed to friction*, which are especially involved, and in which the changes usually commence. Thus, in the aortic valves it is the convex surfaces of the segments which are most liable to be affected, and not the free edge of the segment, but the little band of tissue which passes from its attached border to the corpus Arantii in the centre (Fig. 117), and in the mitral valve the auricular surface of the segments at a little distance from the attachment of the chordæ tendineæ (Fig. 118). When portions of the endocardium, apart from valves, are affected, it often seems to be due, as Dr. Moxon pointed out, to the irritation caused by the friction of vegetations or fibrinous clots situated on the valves themselves; but it is probable that infection of the surface by organisms from the valve-lesion plays the chief part (Fig. 119).

The histological changes accompanying endocarditis resemble those already described as occurring in those more chronic forms of arterial inflammation known as atheromatous. The endocardium and inner coat of an artery are very analogous in their structure, both being non-vascular and consisting of a layer of connective tissue with an internal endothelial covering. The inflammatory process may be acute or chronic.

Fig. 119.

Endocarditis due to Friction. The drawing represents a long vegetation on one of the segments of the aortic valve, which by rubbing on the endocardium below has produced numerous inflammatory granulations (A).

ACUTE ENDOCARDITIS. — If the process be acute, the deeper layers of the endocardium become rapidly infiltrated with young cells, and as these increase in number the intercellular substance becomes softened and destroyed; and thus is produced a soft tissue composed almost entirely of cells, such as always results from inflammatory processes in connective tissue. The new tissue as it increases projects through the superjacent endothelium in the form of minute granulations and vegetations upon the surface of the softened valve. (See Figs. 117 and 118.) The

endothelial elements are said by some to participate in the active process. This is the **papillary** form of the disease.

The above changes take place in an almost non-vascular tissue, and, although there is more or less increase of vascularity in the external endocardial layers, where the capillaries are more numerous, there is rarely any redness or injection of the endocardium seen after death. The granulations, rough and bereft of endothelium, frequently induce coagulation upon themselves, and become covered by fibrinous caps. These must not be confounded with the vegetations themselves (Fig. 120).

The results of this cellular infiltration vary. If the process be very intense, the new tissue may break down, and thus a loss of substance result—an endocardial **ulcer**. This takes place without any accumulation of cells sufficient to form an abscess, the new tissue simply becoming rapidly softened and disintegrating; but in rare cases small quantities of pus are found in the deeper endocardial layers (**abscess**). The ulcer is irregularly defined, and its edges are usually swollen and thickened. This **ulcerative endocarditis** is, however, not frequent, the process usually being less acute. The ulceration may lead to perforation of the valve or to a considerable destruction of its substance. Laceration or aneurism of the valve may also ensue from the pressure exercised by the blood against the damaged tissue. Sometimes the ulcerative process extends so as to involve the cardiac substance. Ulcerative endocarditis is a grave affection, often giving rise to embolism and sometimes to a pyæmic process.

Fig. 120.

Acute Endocarditis. A granulation from the mitral valve, showing a fibrinous coagulum upon the surface of the granulation. × 10. (Rindfleisch.)

When the inflammatory process is less intense, as is much more commonly the case, the granulating valves may adhere to each other or to an inflamed patch on the wall of the heart. The new tissue becomes incompletely organized into a fibrillated structure, whilst it undergoes, in part, fatty and calcareous degeneration. These changes always produce permanent **thickening, rigidity,** and **shrinking** of the valves, and consequent insufficiency or stenosis, or both. The new tissue may continue to grow after the severity of the process has subsided, and thus are produced the vegetations and papillary excrescences on the valve which are so commonly met with. (See Fig.

119.) These consist of a lowly-organized tissue which tends to undergo fatty and calcareous changes.

Etiology.—Endocarditis occurs especially in acute rheumatism; also in pyæmia, puerperal fever, gonorrhœal rheumatism, scarlatina, typhoid, and chronic Bright's disease. The papillary form is by far the commoner. The ulcerative may occur primarily, but as a rule supervenes upon the papillary or chronic forms.

The relation of endocarditis to the above diseases, and the course of the ulcerative forms, suggest an infective origin. In ulcerative endocarditis many observers have found micrococcus colonies on the vegetations and in the substance of the valves; Köster and Klebs found them also in the papillary form. In some cases bacilli also have been found. In five cases of primary ulcerative endocarditis examined by B.-Hirschfeld cocci only were present in all; and these organisms are demonstrable also in the secondary inflammations. In some cases no fungi have been found. No positive conclusion can be arrived at with regard to the etiology of the disease without culture- and inoculation-experiments. Wyssokowitsch and others state that ulcerative endocarditis may be produced in animals by injecting into the blood a very large dose of pyogenic cocci, or by a moderate dose if the valves are previously torn and bruised by a rod passed through the jugular vein into the heart.

CHRONIC ENDOCARDITIS.—This may be the sequel of acute inflammation, or the process may from its commencement be chronic in its nature. Conditions of mechanical strain, such as lead to chronic endarteritis, are the most important causes of chronic inflammation of the endocardium. The cell-infiltration is much less rapid and abundant than in the acute form; the intercellular substance consequently becomes much less softened and destroyed, and the new tissue has a much greater tendency to develop into a fibrillated structure. The result of these chronic processes is the production of a **fibroid thickening** of the endocardium, with more or less induration and contraction of the valves, narrowing of valvular orifices from adhesion of adjacent valves from their bases toward their apices, and shortening and thickening of *chordæ tendineæ*. The new tissue sometimes forms papillary growths on the valves, which undergo partial fatty and calcareous changes. (See Fig. 119.)

Myocarditis.

Myocarditis, or inflammation of the cardiac substance, is much less frequent than the preceding. Intense and concentrated inflammations leading to the formation of abscess probably occur only as the result of a pyæmic process. Less intense and more diffuse forms of cardiac inflammation are also not unfrequently met with in association with pericarditis, and less commonly with endocarditis. Here

Fig. 121.

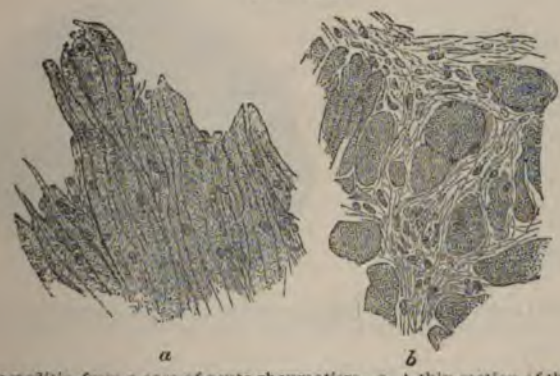
Acute Myocarditis extending from the Pericardium. A vessel is shown around which there is marked infiltration of fluid and cells, both white (faint clots) and red (black clots). The fibres are structureless and hyaline: death was sudden.

the inflammatory process appears, by extension, to involve the immediately adjacent muscular layers of the organ, which are found infiltrated with small cells, the fibres themselves being softened and granular; or the fibres may be clear and structureless from coagulation-necrosis (p. 271).

In addition to the above a form of myocarditis must be recognized in which the substance of the heart becomes more generally involved. In certain cases of acute rheumatism the muscular tissue of the heart is found after death swollen, softened, opaque, and occasionally faintly mottled with slightly yellowish patches. When examined microscop—

ically the fibres are seen to have lost their striation and to be finely granular, their nuclei are large and prominent, and small cells are found in varying numbers infiltrating the intermuscular tissue (Fig. 122). I have met with these appearances in two or three cases of

FIG. 122.



Acute Myocarditis, from a case of acute rheumatism: *a*. A thin section of the left ventricle made in the direction of the muscular fibres, showing the granular and swollen condition of the fibres and the prominence of their nuclei. *b*. A transverse section, showing the cellular infiltration of the intermuscular tissue. × 200.

acute rheumatism, and they must, I think, be regarded as evidence of an acute inflammatory process. The change is most marked in the left ventricle, and it is usually associated with endo- or pericarditis. It is a grave complication of acute rheumatism and perhaps of some other diseases; it is probably more frequent than is generally supposed.

FIBROID INDURATION OF THE HEART.—This, a comparatively rare condition, is probably, in most cases, a result of chronic myocarditis. The change is characterized by the development of a fibrillated tissue between the muscular elements. The process commences in the intermuscular septa around the blood-vessels. These become infiltrated with small cells, which tend to develop into connective tissue (Fig. 123). The growth of new tissue gradually extends between the bundles of muscular fibres, so that ultimately each fibre may be surrounded by a tract of dense fibroid tissue (Fig. 124). The muscular fibres themselves, owing to the resulting interference with their nutritive supply, atrophy, undergo fatty metamorphosis, and are gradually replaced by the fibroid growth (Fig. 124). Very frequently the cellular nature of the growth which I

believe to characterize the earlier stages of its development is not seen, the new tissue being simply fibroid. Thus, Dr. Hilton Fagge in a series of eleven cases of fibroid disease of the heart found that cellular elements in the new growth were almost invariably absent.[1]

Fig. 123.

Fig. 124.

Fig. 123.—Fibroid Induration of the Heart. A thin section from the wall of the left ventricle, showing the small-celled growth in the intermuscular septa around the blood-vessels. *a*, *a*, vessels. × 200.

Fig. 124.—Fibroid Induration of the Heart. A section from left ventricle of the same heart as Fig. 123, showing a more advanced stage. The fibroid tissue surrounds the individual muscular fibres, which are undergoing fatty degeneration. × 200.

Fibroid induration of the heart appears in many cases to be induced by inflammatory processes commencing in the peri- or endocardium. When secondary to pericarditis, the change is usually most advanced in the more external portions of the cardiac walls, and it commonly affects both the right and left ventricles. When, on the other hand, an endocarditis is the precursor of the indurative process, the change is more marked in the internal muscular layers, and, inasmuch as inflammatory processes in the endocardium occur almost exclusively in the left cardiac cavities, the left ventricle is principally involved. In other cases the fibroid growth appears to be the result of syphilis. (See "Syphilis.")

Although the growth of new tissue is thus usually more advanced in certain portions of the muscular walls than in others, it is by no means uniformly distributed. In some parts it may be very dense, the muscular fibres being entirely obliterated, whilst in others it is entirely wanting and the muscular elements present a normal appearance.

The cardiac walls may become much thickened by the new growth, and the induration of texture is often very considerable. In the specimen from which the accompanying drawings were made the walls

[1] See *Trans. Path. Soc. Lond.*, vol. xxv. p. 64.

of the left ventricle were so hard that they cut almost like a piece of tendon.

Fibroid induration of the heart, excluding that resulting from syphilis, appears to occupy the same pathological position as similar fibroid changes in other organs—*e. g.* in the liver and kidneys. It must therefore be regarded as the result of a chronic inflammatory process—a chronic myocarditis. Its effect must evidently be to interfere very materially with the motor power of the organ, and it consequently constitutes one of the most grave of all the cardiac diseases.

CHAPTER XXXIX.

INFLAMMATION OF LYMPHATIC STRUCTURES.

INFLAMMATORY processes in lymphatic structures usually result from their injury by substances conveyed to them by the lymphatic vessels. They include **acute** and **chronic** inflammations and the specific inflammations associated with **typhoid fever**. Each of these must be considered separately.

ACUTE INFLAMMATION OF LYMPHATIC STRUCTURES.

Examples of acute inflammation of lymphatic structures are furnished by the inflammation of the glands in the axilla from a wound on the hand, of the glands in the groin from soft chancre, and of Peyer's and the solitary glands in the intestine from inflammation of the intestinal mucous membrane.

Inflammation of lymphatic glands is almost always due to absorption of some infective substance from a primary focus of inflammation (diphtheritic, erysipelatous, scarlatinal, chancrous, etc.); micro-organisms have frequently been demonstrated in them. A gland affected by acute inflammation becomes intensely vascular and the seat of free exudation. The escaping leucocytes accumulate in its tissues and sinuses until all distinction between medulla and cortex has disappeared and the gland-substance is soft and pulpy and perhaps strewn with hemorrhages. Leucocytes in the lymph coming from the primary focus are also detained in the gland.

Upon the removal of the injurious influence the process may

gradually subside, the new elements undergo disintegration and absorption, and the gland returns to its normal condition (**resolution**).

In other cases the process goes on to **suppuration**, the trabeculæ are destroyed, many of the cells become disintegrated, and the loculi of the gland become filled with pus. This is usually associated with inflammation and suppuration of the surrounding connective tissue. In the glands of a mucous membrane the process gives rise to what is known as a follicular abscess. In still more acute cases the inflammation may be truly hemorrhagic.

Chronic Inflammation of Lymphatic Structures.

Chronic inflammations of lymphatic structures result from injuries which are less severe and more prolonged in their action than those which give rise to the acute form. The resulting cellular infiltration of the gland is consequently a more continuous one, and the gland becomes more or less permanently increased in size. The reticulum is also considerably involved. These chronic inflammatory processes differ from the acute, inasmuch as they lead to a gradually increasing development of the reticular structure of the gland. The reticulated network becomes thicker and more fibrous, its meshes become smaller and smaller, the lymph-cells diminish in number, and thus the gland becomes hard and fibrous in consistence (Fig. 125). Perhaps in these chronic cases the cells of the gland-substance and the flat connective-tissue cells covering the trabeculæ multiply and assist in forming the infiltrating cells, but it is difficult to prove. Fatty patches are frequent in chronically inflamed glands.

Fig. 125.

Chronic Inflammation of a Lymphatic Gland, showing the increase in the stroma and the diminution in the number of the lymphoid cells. × 200.

Scrofulous Glands.—In those chronic inflammations of the lymphatic glands which occur in scrofulous subjects, and in which the glands tend to become caseous, the changes resemble those which have been already described as characteristic of scrofulous inflammation (Chap. xxxii.). The cell-infiltration is considerable, there is but little tendency to absorption, and many of the cells increase in size, and even form multinucleated elements. The gland thus becomes

enlarged, soft, and elastic in consistence, and of a uniform grayish-white color. Owing partly to obstruction of the circulation caused by the pressure of the cell-infiltration, the gland undergoes retrogressive changes and becomes caseous. The caseous material may subsequently liquefy or become infiltrated with calcareous particles. The great majority of caseous lymphatic glands are tuberculous, and the Bacillus tuberculosis is found in them in small numbers.

Inflammation of Lymphatic Structures in Typhoid Fever.

Typhoid fever is an acute general infective disease, the cause of which is probably a bacillus discovered by Koch and Eberth independently, and described in the chapter on micro-organisms. Many believe that infection occurs from the intestine and that the intestinal lesions are points of inoculation; but there is no proof of this, and there does not appear to be any constant relation between severity of intestinal ulceration and severity of the disease, patients with extensive ulceration being sometimes able to attend to their business until suddenly struck down by perforation or hemorrhage.

The ordinary course of the fever lasts three to four weeks, and the temperature as a rule both rises and falls (*lysis*) gradually. The most characteristic lesions are found in masses of lymphoid tissue, especially the solitary and agminated follicles of the intestine, the corresponding lymphatic glands, the spleen, and sometimes the red marrow: the intestinal lesions are the most constant, and their pathological state may be said roughly to advance with the clinical state, so that we can guess at the state of the intestine from the symptoms and the day of the disease.

The pathology and morbid anatomy of typhoid fever include more than the lesions of the above-mentioned organs. First, there is the evidence of general poisoning in the shape of the continued fever, which may assume a septic type, and even be accompanied by septic abscesses, probably resulting from a mixed infection. Naturally, in so long a fever cloudy swelling (p. 77) of organs is marked. Not uncommonly waxy degeneration of muscle (p. 81) is found. Endocarditis is rare. Ulceration of the larynx, especially about the epiglottis, perhaps leading to œdema glottidis or to necrosis of cartilage, is occasional. Bronchitis is usual, and broncho-pneumonia may supervene; œdema of the lungs is common in fatal cases; lobar pneumonia is a rather frequent complication in some epidemics.

We shall now describe specially the morbid conditions found in the lymphatic apparatus.

The Spleen.—In the spleen the change resembles that which occurs in many of the other acute febrile diseases, although it reaches its maximum in typhoid: it may be absent, especially in the older class of patients. The splenic tissue becomes exceedingly vascular, and the lymphatic elements increase rapidly in number, so that the organ often attains two or three times its natural size: the capsule becomes tense, the section dark red; the consistence is fairly firm at first, but softening occurs in two or three weeks; the section is swollen, dark, and opaque-looking; the Malphigian bodies are often prominent and enlarged. Many of the new elements enter the blood, thus causing a slight temporary increase in the number of white blood-corpuscles. Large corpuscles containing normal or altered red corpuscles may be numerous, and similar cells have been found in the blood. As the fever subsides (fourth week) the hyperæmia diminishes, many of the new elements undergo disintegration and absorption, the remainder enter the blood, and thus the organ regains its normal characters and dimensions.

The Intestinal Lymphatic Structures.—It is in the solitary and Peyer's glands that the most characteristic changes in typhoid fever take place. In most cases the process is limited to those in the ileum and cæcum; and those glands are always most affected which are situated nearest to the ileo-cæcal valve. The cæcum is involved in one-third of the cases; ulcers may be found in the rectum, but in the great majority of cases they do not go lower than the ascending colon. It is unusual to find ulcers higher than nine feet above the valve, but they may extend even into the upper part of the duodenum. The primary change here consists in a hyperæmia and cell-infiltration of the glands. Many of the cells increase considerably in size, so as to form the multinucleated elements already alluded to. Both Peyer's patches and the solitary glands thus become considerably enlarged and prominent, standing up above the surface of the intestine, sharply circumscribed, sometimes even overlapping their base a little, and

Fig. 126.

Typhoid Swelling of Peyer's Patches and Solitary Glands of the Intestine.

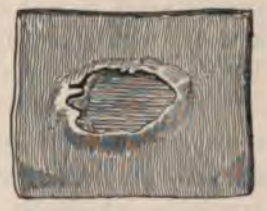
surrounded by special hyperæmia (Fig. 126). They are of a grayish-white or pale-reddish color, and of a soft, brain-like consistence, hyperæmia varying inversely as the swelling. The surrounding mucous membrane is also exceedingly vascular, and is the seat of an acute general catarrh, which is most pronounced before the glands swell. The cellular infiltration in many parts rapidly extends beyond the confines of the glands into the immediately surrounding and subjacent tissues, and in some cases even into the muscular and serous coat. This carries us up to the eighth or twelfth day of the disease.

The process now passes into the second stage, that of the death and disintegration of the newly-formed tissue. This may terminate in various ways. Many of the enlarged glands subside, the new elements become fatty and are absorbed, and the inflammation thus undergoes a gradual process of **resolution.** In others the individual follicles of the gland rupture, discharging their contents externally, and the patches then acquire a peculiar reticulated appearance. The most characteristic termination, however, of the typhoid process is the separation of the dead tissue as a slough and the formation of the **typhoid ulcer.**

Resolution or necrosis occurs from the tenth or twelfth to the fifteenth or sixteenth day, and in the case of necrosis the slough separates toward the end of the third or beginning of the fourth week. This is the period of danger during which fatal **hemorrhage** may occur—some vessel not being securely closed before the separation of the slough, or the thrombus being mechanically displaced—or **perforation** into the peritoneum take place.

The process of sloughing and ulceration may, like the cell-infiltration, take place uniformly throughout the whole gland, in which case the whole mass is thrown off, leaving an ulcerated surface corresponding in size with that of the gland (Fig. 127). More commonly, however, the sloughing commences in different portions of the patch, and small irregular losses of substance result, which may gradually extend until they form one large ulcer.

FIG. 127.



A Typhoid Ulcer of the Intestine.

Although, as already stated, the cell-infiltration may extend beyond the confines of the glands, this is rarely the case with the ulceration. The peripheral infiltration undergoes resolution, and

hence the ulcers have the same configuration as the original glands, those originating from the patches being oval, with their long diameters in the direction of the gut, and those originating in the solitary glands being spherical in shape, as also are those from partial sloughing of a patch. In rare cases when there is much infiltration of the surrounding mucous membrane the ulceration may extend slightly beyond the confines of the glands. An ulcer from a single Peyer's patch may be five inches long: by the blending of patches and follicles, and by the large number affected in the neighborhood of the ileo-cæcal valve, the surface here may seem almost deprived of mucous membrane.

With the sloughing and disintegration of the new tissue the process of infiltration ceases, and hence there is no induration or thickening of the base or edges of the ulcer. The base is smooth, and is usually formed of the submucous or muscular coat of the intestine. The edges are usually thin and undermined, and consist of a well-defined fringe of congested mucous membrane (Fig. 128). This is best seen

Fig. 128.

A Typhoid Ulcer of the Intestine (diagrammatic), showing the undermined edges of the ulcer and the slough still adherent. *a*. Epithelial lining. *b*. Submucous tissue. *c*. Muscular coat. *d*. Peritoneum.

when the gut is floated in water. In some cases, especially where there is surrounding infiltration, the edges are firm and thick. In others, again, the sloughing extends deeper through the muscular layer to the peritoneum, which either sloughs or is burst by some muscular effort, either of the bowel stimulated by improper food or of the abdominal muscles when the patient is allowed to use them strongly. The perforation is generally small, the peritoneum being usually bared to only a small extent. Diffuse peritonitis (purulent) as a rule results: rarely adhesions form and localize the inflammation. Peritonitis may occur also by simple extension from the gut, from an inflamed gland, or from a splenic abscess.

The third stage of the process is that of cicatrization, which usually begins in the fourth week. This takes place by the resolution of the peripheral infiltration, the approximation and union of the undermined edges with the floor of the ulcer, and the gradual formation from the margin of an epithelial covering. The gland-structure is not regenerated. The resulting cicatrix is slightly depressed, pig-

mented uniformly or only around the margin, and less vascular than the surrounding mucous membrane. There is no puckering or diminution in the calibre of the gut. In some cases, however, cicatrization does not take place so readily, and the floor of the ulcer becomes the seat of a **secondary** ulceration. This usually takes place after the general disease has run its course or during a relapse. Profuse hemorrhage and perforation more commonly result from the secondary ulceration than from the primary sloughing of the glands. Only one ulcer may be affected by this secondary process, the rest being healed or healthy.

The Mesenteric Glands.—The change in the mesenteric glands is probably secondary to that in the intestine. These glands become the seat of an acute cellular infiltration, and are enlarged, soft, and vascular. They usually, like many of the glands in the intestine and the spleen, undergo a gradual process of resolution. In rare cases, however, the capsule of the gland is destroyed, and the softened matters may escape into the peritoneal cavity, and so cause peritonitis. The enlarged glands may also become caseous and subsequently calcified.

The Marrow.—Ponfick has shown that in typhoid the marrow of bones, like the splenic *pulp*, may contain large cells, in which may be as many as twenty-five red corpuscles: these break down, and in the convalescent stage the large cells contain only pigment.

CHAPTER XL.

INFLAMMATION OF MUCOUS MEMBRANES.

INFLAMMATIONS of mucous membranes are divided into **catarrhal, croupous,** and **diphtheritic.**

CATARRHAL INFLAMMATION.—This may, according to its intensity, be serous, mucous, muco-purulent, or purulent. Acute cases begin with redness, slight swelling, and abnormal dryness of the mucous membrane, some tenderness of the part, and perhaps pain. After a time this is succeeded by exudation, and the symptoms are then, as a rule, relieved. In chronic cases the symptoms and physical signs are much less marked, the exudation being generally the first thing noted.

Post-mortem, all hyperæmia has generally disappeared and the membrane may look paler than natural; but after chronic inflammation of any intensity more or less dark-gray pigmentation, from the hæmoglobin of extravasated red corpuscles, will, in most situations, bear evidence of former inflammation (p. 101). These appearances can be studied nowhere better than in the inflamed bladders from cases of stricture, enlarged prostate, etc.

Serous Catarrh.—Free serous effusion occurs from the vessels and escapes upon the surface; this is often seen in the early stage of colds in the head.

Mucous Catarrh is characterized mainly by increased production of mucus, which escapes mixed up with serous fluid or remains adherent to the surface, as is often seen in chronic pharyngitis. Sometimes the sero-mucous discharge is tolerably clear, at others more or less opaque; in the former case only a moderate number of cell-forms are present—in the latter, many. Most of the cells are escaped leucocytes, but many are desquamated epithelial elements. The increased "secretion" of mucus and the excessive desquamation of epithelium have been looked upon as disproving the view that depression of function is an invariable result of inflammation. The formation of mucus, however, is much more a degeneration than a secretion, and such a process might well be hastened by irritation. With regard to the epithelial cells, it would seem likely that whilst the superficial layers are killed by the irritation and cast off, the deeper ones are more resistant even than the elements of the superficial vessels. The action of an irritant which causes the latter to leak gravely leaves the former able to multiply freely. Indeed, it is conceivable that what would be an irritant to one cell might be a stimulant to another more resistant organism, rendering it more capable of utilizing increased supply of food.

Purulent Catarrh.—If the inflammation be more intense, the escape of leucocytes is still greater and the secretion becomes purulent. As the exudation approaches more and more closely the character of true pus, the formation of mucus and the desquamation of epithelium cease, a **muco-purulent** stage being often passed through.

A section through a mucous membrane thus affected (Fig. 129) shows desquamation of the superficial epithelial cells, and these often contain broods of young cells—leucocytes which have migrated into them. Leucocytes lie here and there between the deeper cells, in which evidence of multiplication will be found. More or fewer whit

corpuscles infiltrate the mucosa, together with fluid exudation, producing swelling of it, or thickening and induration if they go on to form connective tissue.

Simultaneously, all lymphoid structures in the mucous membrane are affected. The lymph-follicles swell, and their contents may soften

FIG. 129.

Catarrhal inflammation of the Conjunctiva: *a.* Epithelium. *b.* Infiltrated subepithelial connective tissue, showing the desquamation of the epithelium and the young elements within the epithelial cells. (Rindfleisch.)

and form minute abscesses, which burst and leave the small ulcers (follicular) so often seen in catarrhal conditions of the intestines and pharynx. The ulceration in some cases extends beyond the confines of the follicle. The proper glandular structures also may become involved. Their epithelium multiplies, the glands become choked with the epithelial elements, and they may subsequently atrophy. This is seen in catarrh of the stomach.

The acute process may quickly subside or it may become chronic. In the latter case the hyperæmia diminishes, but the escape of leucocytes and the multiplication of the epithelial elements continue, and the subepithelial tissue becomes more extensively infiltrated with small cells.

Chronic catarrhal inflammations of mucous membranes differ from the acute, inasmuch as the subepithelial connective tissue is often extensively infiltrated with small cells which may ultimately form an imperfectly-fibrillated structure. The membrane thus becomes indurated and thickened, and the pressure exercised by the new growth may induce atrophic changes in the glandular structures which it contains, as is seen in chronic catarrh of the stomach; by preventing the exit of their secretion it may cause them also to dilate so as to form cysts. These changes in the subepithelial connective tissue are usually accompanied by enlargement of the lymphoid structures—an

enlargement which sometimes gives to the membrane a nodular or granular appearance. This is well seen in the pharynx (*follicular pharyngitis*). The enlarged lymphoid structures may ulcerate and constitute the starting-point of an infective process. (See "Tuberculosis of Mucous Membranes.") In some situations, as the stomach and intestine, the membrane often at the same time becomes deeply pigmented.

CROUPOUS AND DIPHTHERITIC INFLAMMATION.—These terms are applied to inflammations of mucous membranes and raw surfaces which lead to the production of a so-called **false membrane**—such as is seen, for example, in croup. The formation of this fibrinous layer upon the surface of the membrane is quite characteristic, and at once distinguishes this form of inflammation from a simple catarrhal process. On mucous surfaces the membrane may exist in little patches or cover a large area; it is usually of a yellowish- or grayish-white color, and in consistence varies from a firm and tough to a soft pultaceous material. It may be deeply bloodstained. It is with greater or less difficulty separable from the subjacent tissue, which in all cases after its removal is found to have lost its epithelium. In thickness it may vary considerably in different parts. The two words "croupous" and "diphtheritic" owe their origin to the belief, still held by many, that there is an idiopathic membranous inflammation of the larynx (croup) distinct from diphtheria. Croup had long been known when Bretonneau in 1826 first accurately described diphtheria, gave the disease its present name, and asserted that "croup" was merely laryngeal diphtheria. The term is used with this meaning in France, and the majority of English physicians adopt Bretonneau's view. The adjectives "croupous" and "diphtheritic" are often used as synonymous, but many propose to speak of a membrane as **croupous** when it involves no more than the epithelium of a mucous membrane, and as **diphtheritic** when it involves the mucosa. These differences in the depth of the tissue involved are probably due to variations in the intensity of the process; and, according to Cohnheim, the process is more likely to be superficial in those situations where a distinct basement membrane exists, as in the pharynx and respiratory tract, than in those where this is not the case, as in the intestines and conjunctiva. A false membrane, superficial to the basement membrane, is much more easily detached than one which involves this structure.

Others would limit the term "croupous" to false membranes formed chiefly of coagulated fibrin, whilst "diphtheritic" is applied to those consisting of tissues which have undergone coagulation-necrosis (p. 271). This division, which renders "croupous" equivalent to "fibrinous," seems to be the better, although the two processes—coagulation of fibrin and of cells—are closely allied, and one may succeed the other in the same case.

The relative rarity of fibrinous inflammations of mucous as compared with serous membranes led Weigert to investigate the reason of the difference. He found that inflammatory exudations from mucous membranes coagulated so soon as the epithelium was destroyed; and he started the hypothesis that *living* epithelium, like endothelium, prevents the formation of fibrin.

But the injury which causes destruction of epithelium must be more intense than one which does not cause such damage; and it is likely that the exudation in the former cases will be more highly fibrinous than in the latter. Now, in a case of true diphtheria a patch of epithelium and more or less of the subjacent tissue are killed by the irritant and undergo coagulation-necrosis; and, if the false membrane thus formed be removed, a fresh one will appear rapidly, which, unless the destruction of tissue extends, can hardly consist of anything but coagulated fibrin.

The two kinds of membrane differ microscopically. The fibrinous has the appearance of lymph—a network of fibrin containing in its meshes a greater or less number of leucocytes, desquamented epithelial cells, and débris; it is easily stripped off. The diphtheritic membrane is separated less easily, and, if deep, only with great difficulty. Superficially, it closely resembles the croupous membrane, but the deeper parts consist of much-swollen, homogeneous cells from which the nuclei have disappeared. There is no sharp line in advancing cases between the coagulated and the living tissue-elements. These membranes resist acetic acid much longer than do the simple fibrinous ones.

False membranes probably form occasionally upon every mucous membrane, and obviously from very different causes. Examples are—the membranes which form on the tonsils, larynx, etc. in true diphtheria; from scalds and the application of caustic chemicals; in the bladder after parturition (when a complete cast may be expelled) and in the most acute cystitis; in the vermiform appendix, sometimes from the irritation of a concretion; in the lower part of the large

intestine in dysentery; and in the air-tubes in plastic bronchitis. It may be noted here that false membranes sometimes form upon granulating wounds (croup of granulations), and it is held by some that there is no line between such cases and those of true diphtheria of wounds and of hospital gangrene. It seems most probable, however, that there is an etiological difference, for croup of granulations may be induced at will by blistering the surface.

Although the above facts show that false membranes may result from the action of simple irritants, the great majority met with in man are due to infective poisons—*e. g.* diphtheria, diphtheritic conjunctivitis, epidemic dysentery—all highly contagious. Micrococci with other organisms are found in clouds and zooglœa masses in almost all cases, but no etiological connection has been established between them and any of these diseases.

Dysentery.

The inflammatory processes occuring in the intestine in dysentery are for the most part limited to the large intestine, although the ileum is also occasionally involved. The inflammation is always most marked in the rectum and descending colon, and it may be stated generally that it is characterized by ulceration and sloughing of the mucous membrane.

The intestinal changes vary considerably according to the intensity of the inflammatory process. In the milder forms of the disease the changes are most marked on the summits of the folds of the mucous membrane. These are found covered with a grayish-white layer of fibrinous-looking material, which when scraped off leaves a superficial loss of substance. The mucous membrane generally is hyperæmic and softened. The submucous tissue also is infiltrated with inflammatory products, and the solitary glands are enlarged and prominent.

When the process is more severe the submucous tissue becomes more extensively involved and the superficial layer of fibrinous material extends over wider areas and implicates more deeply the mucous membrane. The thickening of the intestinal wall, however, is much greater in some parts than in others, so that projections are produced upon the inner surface of the intestine corresponding with those parts which are the most affected. The enlarged solitary glands usually slough, and so give rise to circular ulcers which rapidly increase. When the process has reached this stage the muscular and

serous coats are implicated, the latter being covered with layers of fibrin which form adhesions with adjacent parts. The intestine is much dilated, and contains blood and disintegrating inflammatory products.

In the most intense forms of the disease the necrosis is more extensive. According to Rokitansky, large portions of the mucous membrane are converted into black rotten sloughs. The submucous tissue is infiltrated with dark blood and serum, but subsequently it becomes the seat of a reactive suppurative inflammation by means of which the necrosed portions of tissue are removed.

If death does not occur and the inflammatory process subsides, the ulcers may gradually heal. When the loss of substance has not been considerable, the edges of the ulcers may, by the contraction of submucous tissue, become completely approximated. More commonly, however, the loss of substance is so great that portions of the membrane are left, consisting simply of connective tissue.

When the inflammatory process becomes chronic the changes in the submucous connective tissue become more marked, and the new fibroid growth gives rise to considerable thickening and induration of the intestinal wall and to more or less contraction and narrowing of the cavity. Sometimes it forms fibrous bands which project into the gut. The formation of abscesses and fistulous passages thickened in the intestinal wall occasionally occurs.

CHAPTER XLI.

INFLAMMATION OF SEROUS MEMBRANES.

INFLAMMATORY processes in serous membranes vary in their intensity and in the amount and character of the effusion.

The process commences, as in mucous membranes, with hyperæmia, and exudation of fluid and of blood-corpuscles into the serous cavity quickly follows (Fig. 130).

Next to hyperæmia, the first sign of inflammation is a loss of polish of the surface, owing partly to the injury done to the epithelium by the irritant, and to the passage out through the layer of cells of the exudation, partly to the presence of leucocytes and a little fibrin on the surface. The moistening of the surface with the albuminous

exudation renders it "greasy." As the inflammation goes on the surface becomes opaque, roughened, and exceedingly vascular, and soon it becomes covered with a fibrinous layer, whilst more or less liquid transudes into its cavity. The coagulable material which exudes from the vessels forms a soft, elastic, membranous, or reticu-

FIG. 130.

Inflamed Epiploon of a Rabbit, showing changes in the endothelium. × 250. (Cornil and Ranvier.)

lated investment enclosing in its meshes numerous small cells. This either glues the two surfaces of membrane together, collecting especially where pressure is least—viz. in the angles along lines of contact of the intestines, where injection also is most marked—or, if they are separated by liquid effusion, forms a slightly adherent layer (Fig. 131). The exuded liquor varies considerably in amount, and

FIG. 131.

Inflammation of the Diaphragmatic Pleura, showing the adherent fibrinous layer: *a*. Muscular coat of diaphragm. *b*. Subserous tissue. *c*. Serous membrane. *e*. Fibrinous layer. × 400. (Rindfleisch.)

is always turbid, thus differing from non-inflammatory effusions. It contains flakes and masses of coagulated fibrin and innumerable cells, the latter being, in the earlier stages of the process, almost entirely emigrants.

The nature of the subsequent changes will depend upon the inten-

sity of the inflammation and upon the amount of liquid exuded into the serous cavity. If the inflammatory process subsides, and the liquor exuded is not sufficient to prevent the two surfaces of the membranes from coming into contact, they grow together and form an **adhesion**. This constitutes the so-called **adhesive inflammation**. The union is effected by the formation of connective tissue (p. 260). This is by far the most frequent form of inflammation of serous membranes. The process is precisely similar to that which takes place in the union of an incised wound. It is probable also that in some cases union may take place without the intervention of any fibrinous layer, by the formation and growing together of irregular papillary outgrowths from the subendothelial tissue.

If, however, the inflammatory process is severe or the surfaces of the membrane are separated by a large quantity of liquid effusion, organization and adhesion cannot be effected. If a large quantity of liquid exists in the serous cavity, the removal of this becomes necessary before union can take place. If the intensity of the irritant is considerable and its action prolonged, union is prevented by the formation of pus. These two conditions must be considered separately.

The existence of a large amount of effusion prevents approximation, and therefore adhesion, of the serous surfaces, and before this can be effected absorption of the liquid becomes necessary. The presence of the liquid itself, however, interferes with its absorption. This is owing, as already stated (p. 269), to the pressure which it exercises upon the blood-vessels and lymphatics; which pressure, by hindering the circulation in these vessels, tends not only to prevent absorption, but also to interfere with the restoration of the vascular walls to a normal state, and so favors a continuance of the exudation. The removal of some of the liquid by artificial means consequently facilitates absorption of the remainder. When the process is protracted the subendothelial connective tissue becomes involved and infiltrated with small cells, and a richly vascular granulation-tissue is formed beneath the layer of proliferating endothelium. The endothelium itself becomes less abundant, and if the inflammation subsides the new granulation-tissue gradually develops into connective tissue, and thus a false membrane is formed, rich in vessels, which takes the place of the endothelial layer. As the liquor is absorbed the two surfaces of the membrane come into contact and grow together, the new vessels becoming gradually obliterated.

If the inflammatory process does not subside or is from its commencement of considerable intensity, it may be attended by the formation of large quantities of pus. In this case the exudation of blood-corpuscles is so considerable that the young elements exist in large enough numbers to give to the exuded liquids a purulent character. The condition is then termed **empyæma**. As the connective tissue becomes involved a granulation-tissue is formed, and this may continue to generate pus like an ordinary granulating wound. If the pus be removed, the suppuration may gradually cease, the granulation-tissue develop into a fibrous structure, and the union of the serous surfaces thus be effected. The serous membrane becomes greatly thickened, and the new tissue undergoes considerable contraction in the process of its organization, producing more or less retraction of the chest-wall.

Calcareous plaques of considerable size may develop in adherent parietal pleura.

CHAPTER XLII.

INFLAMMATION OF THE LIVER.

INFLAMMATORY processes in the liver comprise **perihepatitis, abscess,** and **cirrhosis.**

PERIHEPATITIS.

Inflammation of the capsule of the liver, leading to more or less thickening, and often to adhesions with adjacent parts, is met with under various circumstances. Its most common causes are the chronic peritonitis of Bright's disease, chronic alcoholism, and syphilis (Goodhart). The changes are usually slight and of but little pathological import.

In some cases, however, especially in cases of chronic peritonitis (Hilton Fagge), the process is more extensive and leads to marked interference with the functions and circulation of the liver. The whole capsule becomes considerably thickened and gradually contracts, thus causing compression of the organ, which assumes a globular form. The portal circulation is often interfered with by the squeezing process, and ascites with other symptoms of portal obstruction may

result. The liver itself, with the exception of some atrophy and fatty degeneration of its cells, may show no changes; but sometimes it is intersected, and even divided into lobe-like masses, by bands of fibrous tissue passing inward from the capsule. This suggests syphilis as the cause (see p. 343).

Hepatic Abscess.

Acute inflammation of the liver leads to the formation of **abscess.** The abscesses may be **single** or **multiple.** The latter are usually small, but a solitary abscess may attain an enormous size. **Multiple** abscesses are most frequently due to pyæmia or to some inflammatory lesion in connection with the portal system, such as dysentery. In these cases the abscesses are of embolic origin. Inflammation of the bile-ducts, such as sometimes results from gall-stones, etc., and external violence are other causes of suppurative hepatitis.

The **solitary** or **tropical** abscess also is supposed by some to be secondary to some inflammation of the portal viscera. It is known to be often associated with dysentery. It is maintained by many that it is due to a primary hepatitis, and doubtless cases often occur in which no intestinal ulcer or other obvious cause is discoverable. The pathology of this disease is therefore at present obscure.

Cirrhosis of the Liver.

Chronic inflammation of the liver constitutes the condition known as **cirrhosis.** This is characterized by a gradual increase in the connective tissue of the organ, and by the subsequent atrophy of the liver-cells, so that when examined with a low magnifying power the lobules are seen to be separated by new interstitial growth (Fig. 132).

HISTOLOGY.—The process, like that of chronic inflammation in other organs, consists essentially in a cellular infiltration of the interlobular connective tissue of the liver and the development of a more or less highly organized fibroid structure, the number of cells being proportionate to the activity of the process. The new tissue is supplied with new blood-vessels derived from branches of the hepatic artery.

In addition to this cellular infiltration of the interlobular connective

tissue, a proliferation of the bile-ducts is supposed to occur frequently in cirrhosis. This is believed by Charcot to take place in those cases only in which there exists some obstruction of the ducts—the so-called "biliary cirrhosis." (See "Etiology.") Other observers, however,

FIG. 132.

Cirrhosis of the Liver, showing the growth of connective tissue between the hepatic lobules. *a*. Lobules. *b*. New growth of interlobular connective tissue. × 16.

state that new ducts are met with under such various circumstances that their existence is of no value as an indication of the cause. Goodhart doubts the formation of *new* ducts, but thinks the old ones simply become more conspicuous owing to the atrophy of the liver-cells.[1]

The liver-cells are stated by many to undergo active changes and to contribute to the formation of the new tissue. They are in many cases infiltrated with fat, **fatty infiltration** being associated with the cirrhosis. (See Fig. 134.)

The general distribution of the new tissue is described by Charcot as **multilobular, unilobular,** and **intercellular.** In the multilobular form groups of lobules are surrounded; in the unilobular, each lobule; and in the intercellular, the growth invades the intercellular network. These several modes of distribution are frequently associated, all perhaps being found in different parts of the same organ; and although supposed by Charcot to indicate etiological varieties, the differences are probably to be ascribed rather to differences in the activity of the growth: the more active the process, the more uniform and general the distribution.

The effect of the new growth is ultimately to cause atrophy of the hepatic cells and to obstruct the circulation through the portal capil-

[1] The subject is ably discussed by Dr. Goodhart in his "Résumé of Diseases of the Liver," *New Sydenham Soc. Atlas of Path.*, fas. iv.

laries and the passage of bile through the bile-ducts. This effect is materially increased by the process of contraction which the new tissue undergoes. The hepatic cells in the outer zone of the lobules are the first to atrophy. The cells become smaller, often undergo fatty metamorphosis, and ultimately are completely destroyed (Fig. 133). Those in the central parts of the lobule are in the earlier stages but little altered, although they are often stained with bile. As the growth extends, however, these also become annihilated, and the

FIG. 133.

Cirrhosis of the Liver. A thin section from the external portion of one of the hepatic lobules, showing the new growth of connective tissue, and the way in which it involves the intercellular network and causes atrophy of the liver-cells. × 200.

whole lobule may be replaced by connective tissue. The cells in the outer part of the lobules are sometimes, as already stated, infiltrated with fat prior to their destruction. (See Fig. 134.)

PHYSICAL CHARACTERS.—The physical characters of the cirrhosed liver vary. In the earlier stages of the disease the organ is probably always more or less increased in size, the enlargement being almost uniform and the edge rounded and thickened. This enlargement very often exists up to the end of the disease, but in many cases the atrophy of the liver-cells and the contraction of the new tissue lead to considerable diminution in size. The surface of the organ is usually more or less irregular, sometimes "hobnailed," the extent of the irregularity depending upon the distribution of the new tissue and the amount of atrophy that has taken place. Multilobular distribution leads to much greater unevenness of the surface than unilobular. The consistence of the organ is always more or less increased, although in some cases, where the process is very rapid, the increase is so slight as easily to escape observation. Both irregu-

larity of surface and induration are usually most marked along the anterior edge, especially of the left lobe. On section, the new tissue surrounding the lobules, and in many parts completely replacing them, is often visible to the naked eye. This gives to the cut surface a mottled granular appearance, the lobules themselves contrasting with

Fig. 134.

Liver: Cirrhosis with fatty infiltration. × 100, reduced ⅓.

the new interlobular tissue; and this appearance is sometimes increased by fatty infiltration of the cells in the peripheral zone. The capsule also may be thickened, and the organ is frequently stained with bile.

The great increase in the size of the liver which exists in some cases is due in part to a fatty infiltration of the liver-cells (Fig. 134). In those cases also in which the process is rapid, and the new growth consequently very general in its distribution—unilobular and often intercellular—the organ is usually large, death probably supervening before time has been allowed for much atrophy and contraction to take place. Some of the large livers are supposed to be due to obstruction of the bile-ducts, and have been termed "biliary" or "hypertrophic" cirrhosis. The existence of such a condition is disputed by some, especially by Goodhart.

ETIOLOGY.—The great cause of cirrhosis is alcohol. With the

exception of syphilis no other cause can be regarded as proven. The question of a biliary cirrhosis must at present remain an open one. Cirrhosis from syphilis has already been described (p. 342). In the congenital disease the process is often so general in its distribution as closely to resemble some cases of acute alcoholic cirrhosis.

It is important to remember **clinically** that cirrhosis not only obstructs the portal circulation, thus giving rise to ascites, hæmatemesis, diarrhœa, enlargement of the spleen, etc., but that, owing to the destruction of the liver-cells, the glycogenic function of the organ is so much impaired that marked interference with general nutrition results. Jaundice is usually slight, probably because the bile-ducts are not obstructed at various points in their course, but are pretty uniformly compressed from their origin onward.

Acute Yellow Atrophy.

This rare disease of the liver is characterized by a rapid diminution in the size of the organ, accompanied by destruction of the hepatic cells, and is often associated with pregnancy. The liver may, in the course of a few days, be reduced to less than half its natural bulk, being especially diminished in thickness. It is soft and flabby in consistence, bloodless, and of a dull-yellow or yellowish-red color. The lobules are indistinguishable. When examined microscopically, the liver-cells are found to be completely destroyed, being replaced by granular débris, fat-granules, and pigment. Tyrosin and leucin have been found in the disintegrated liver-tissue. The pathology of this disease is exceedingly obscure. By some it has been regarded as a passive degeneration, by others as an acute infective inflammation. Micrococci have been found in the organ in the early stages of the disease by Dreschfeld and others.

CHAPTER XLIII.

INFLAMMATION OF THE KIDNEY.

Inflammatory processes in the kidney present certain variations according to their intensity. They comprise **suppurative, tubal,** and

interstitial nephritis. Of these, suppurative nephritis, as the name implies, is an intense inflammation leading to the formation of abscess, and it is really an acute interstitial inflammation, although the term "interstitial" nephritis is generally applied to chronic processes. It results usually from the transmission of infective materials from some primary lesion (pyæmic), or is associated with some inflammatory condition of the lower urinary passages. Tubal nephritis is also an inflammation of considerable intensity, and in it the structural changes have their principal seat in the urine-tubes. Interstitial nephritis is an inflammatory process which runs a more chronic course, and is of less intensity than either of the preceding; consequently, in it the principal structural changes take place in the connective tissue around the blood-vessels—in the intertubular connective tissue (p. 262). It must, however, be distinctly borne in mind that these two varieties of histological changes—those in the tubes and those in the intertubular connective tissue—*are very constantly associated.* Tubal and interstitial nephritis cannot therefore be separated from one another by any distinct line of demarcation. They might be more correctly designated **acute** and **chronic** nephritis.

Suppurative Nephritis.

Acute inflammatory processes in the kidney attended by the formation of pus give rise to **renal abscesses.** Such processes, as already stated, often result obviously from the transmission by the blood-stream of infective particles from some primary focus, as in pyæmia, or they arise by direct extension from the lower urinary passages. In the latter they constitute what is commonly known as the "surgical kidney.

The abscesses met with in the kidney as the result of pyæmia are confined principally to the cortex, and resemble pyæmic abscesses in other organs. They are usually multiple, and are often surrounded by a thin zone of red hyperæmic tissue. Their size varies from a mere point up to that of a filbert. Their characters have been already described in the chapter on Embolism (p. 230).

SURGICAL KIDNEY.—This is the name commonly given to those inflammatory conditions of the kidney which result from obstructive and inflammatory diseases of the lower urinary passages. They occur frequently in association with renal and vesical calculi,

obstructed ureter, urethral stricture, enlargement of the prostate, etc. These and similar conditions act upon the kidneys in three ways:[1]

1. **By obstructing the outflow of urine from the pelvis.** Regurgitation from the bladder probably never occurs; but as a result of obstruction from any cause more or less of the full force of secretion acts upon the ureter, the pelvis, and the pyramids, and extends along the tubules to their closed ends. This chronic tension is a common cause of chronic inflammation. In cases of obstruction to the outflow from one kidney the changes are limited to it.

2. **By reflexly producing circulatory changes in the kidney.** A close relation seems to exist between the deeper portions of the urethra, the prostate, and the trigone—the parts upon which operations are performed—and the kidneys. An intense hyperæmia due to irritation of the nerves of these parts might in extensively diseased organs lead to arrest of the circulation and death from suppression of urine.

3. **By extension of decomposition from the bladder to the kidneys,** and irritation of the latter by septic products. As regurgitation does not occur, decomposition often remains long limited to the bladder. Extension perhaps takes place along ropy mucus lying as a cord in the opening of the ureter when this has become inflamed from other causes.

The changes in the kidney vary from the most chronic productive inflammation to an acute suppurative process.

Simple long-continued increase of urinary pressure, resulting from some obstruction to the flow of urine, gives rise to chronic renal changes, which are characterized mainly by more or less cellular infiltration of the intertubular connective tissue ("interstitial nephritis"). This cellular infiltration, which is exceedingly irregular in its distribution, occurs both in the pyramids and cortex. The tubules are in some parts found blocked with epithelium, whilst in others they are wasted or obliterated. The walls of the small arteries are not thickened. Owing to these changes the kidneys are somewhat enlarged, the capsule is slightly adherent, the cut surface paler than natural, and the consistence of the organs abnormally tough. As the process advances the pyramidal portions gradually become absorbed, the absorption commencing at the papillæ, and extending until ultimately

[1] The views here expressed are in accordance with the teaching of Marcus Beck: "Nephritis and Pyelitis consecutive to Affections of the Lower Urinary Tract," *Reynolds' System of Medicine*, vol. v.

not only the pyramids, but also the thickened cortex, may disappear, and the kidney be converted into a large cyst divided by fibrous septa into sacculi. If, on the other hand, the urinary obstruction be removed, the processes of inflammation and absorption may cease, and the indurated kidney will then become contracted.

In other cases, when the urinary obstruction is associated with inflammation of the lower urinary passages, the process is much more acute, the cellular infiltration of the intertubular tissue is much more abundant, and leucocytes accumulate in certain situations in such numbers as to give rise to abscesses (Fig. 135). The cortex of a

FIG. 135.

Surgical Kidney. At the lower part of the figure is seen the cellular infiltration of the intertubular tissue and the blocking of the tubes with epithelium and leucocytes. At the upper part there is the commencing formation of an abscess. × 100.

kidney in such a case is thickened, soft, and pale as compared with the deep-red pyramids; its consistence, however, will vary with the presence or absence of chronic interstitial changes. The capsule strips easily, often tearing the substance a little, and exposing on the surface groups of yellow spots usually not larger than a lentil, and each surrounded by a red zone. Many of these contain a drop of pus. On section, yellow streaks are often seen extending from the superficial lesions into the cortex; others exist in the pyramids. The pelvis is generally intensely inflamed.

Klebs described many of the tubules, even the convoluted, as crammed with micrococci. These seem to ascend from the pelvis

along the tubules, distending them greatly and setting up irritative and degenerative processes along their line of passage. When stained with an aniline dye the appearance shown in Fig. 136, from a specimen of Mr. Boyd's, is seen. It is extremely probable that these organisms are the cause of the suppuration. Though very often the urine in the pelvis of such kidneys is septic, it is not necessarily so.

Fig. 136.

Surgical Kidney, showing clouds of micrococci ascending along the tubules. Almost all nuclei have gone from their vicinity. They seem to have caused necrosis or degeneration of the tissues. × about 90.

Tubal Nephritis.

Tubal, parenchymatous, or acute nephritis is that subacute inflammation of the kidney which constitutes the more acute forms of Bright's disease—those which are characterized by a more or less marked beginning, scanty and highly albuminous urine, and dropsy. In its more advanced stages it is the large kidney of chronic Bright's disease.

The changes which take place in the kidney have their seat mainly in the cortex. They comprise increased vascularity and exudation into the urine-tubes, with swelling, and, later, probably proliferation of the tubular epithelium. The prominence of the vascular phenomena, however, varies very considerably in different cases.

In the most acute cases of Bright's disease—those which are induced suddenly, as from exposure to cold—the vascular changes are marked. In these cases the contraction of the cutaneous vessels and the check to the function of the skin caused by the chilling of the surface lead to considerable hyperæmia of the organs. There is abundant exudation into the urine-tubes, many of the capillaries at the same time frequently rupture, and thus there is an escape of blood-corpuscles and of liquor sanguinis into the tubes of the cortex; hence the blood and "blood-casts" in the urine which are so characteristic of the early stages of these most acute forms of the disease.

In this stage the process may quickly subside, and, with the exception of some swelling and desquamation of the tubular epithelium, no further alterations take place in the kidney.

Fig. 137.

Tubal Nephritis. The earlier stage of the process, showing the swelling of the tubular epithelium and some exudation-products in the urine-tubes. In some of the tubes the epithelium has fallen out during the preparation of the section. × 200.

In the less acute cases, those known as chronic Bright's disease with large kidney, the vascular phenomena are less marked and changes in the tubular epithelium are more prominent. The epithelial elements become swollen and granular (Fig. 137). The granules, which are often so numerous as to occlude the nucleus of the cell, are soluble in acetic acid, and thus differ from molecular fat. This is the condition known as "cloudy swelling." Many small cells also are seen within the tubes, and these have been supposed to be the products of epithelial proliferation. It is probable that some of them are thus produced, although the majority must be regarded as having escaped from the vessels. Owing to these changes the tubes become distended with cellular elements (Fig. 138).

Fig. 138.

Tubal Nephritis—a Single Urine Tube, showing the accumulation within the tube. In the few epithelial cells which have escaped is seen the granular condition of the protoplasm. × 200.

In addition to the cell-forms, many of the tubes also contain hyaline cylinders, which are commonly regarded as consisting of coagulated substances which have escaped from the

vessels. By many pathologists, however, this hyaline material is supposed to be the product of a mucoid or some allied metamorphosis of the epithelium. The cell-forms contained within the tubes adhere to this hyaline substance, and some of them are washed away and appear in the urine as "epithelial casts." A varying number of emigrant leucocytes also are usually found around the Malpighian tufts.

The alterations which these changes produce in the physical characters of the kidneys vary according to the extent of the hyperæmia. The organs are always considerably increased in size and more or less abnormally vascular. The capsule separates readily, exposing a perfectly smooth but vascular surface. The consistence is diminished, the tissue breaking with a soft, friable fracture. On section the increase in the size of the organ is seen to be principally due to the increased thickness of the cortex. This is either of a reddish-brown or of an opaque-white or pale-buff color, these differences depending upon the relative proportion of blood and of accumulated intratubular elements. Although in the earliest stage of the most acute forms of the disease the color is redder than natural, it usually becomes pale and opaque. This is owing to the swelling of the epithelial elements and to the accumulation in the cortical tubes. The blood becomes expressed from the intertubular vessels, and hence the increased vascularity is most evident in the Malpighian corpuscles, beneath the capsule, and in the pyramidal portions of the organ. The Malpighian corpuscles stand out as prominent red points, and the pyramidal cones are of a deep-red color, thus contrasting strongly with the pale, opaque cortex.

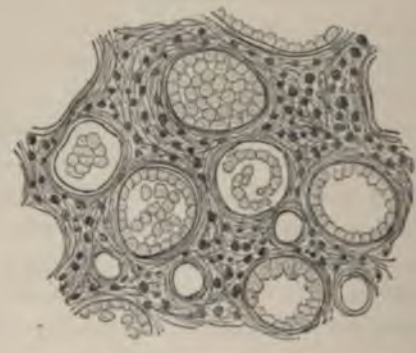
The termination of the process varies. The increased vascularity and epithelial change may, as already stated, subside, and, the inflammatory products passing away in the urine, the organ gradually returns to its normal condition. In other cases the disease continues, and, although the vascularity diminishes, the vitality of the epithelial elements becomes so much impaired that they undergo retrogressive changes. The cells then continue to come away with the urine, adherent to the casts, but instead of presenting a swollen granular appearance, as in the earlier stage of the disease, they contain molecular fat. This fat gradually increases in amount as the degeneration proceeds, until ultimately the cells are destroyed and it appears as free molecules and granules on the tube-casts.

This fatty degeneration of the epithelium is attended by correspond-

ing changes in the appearance of the organ. The redness diminishes and the Malpighian corpuscles are less prominent. The enlarged cortex presents a yellowish-white tinge studded with minute yellowish streaks. This is owing to the presence of fat in the tubes of the cortex. This fatty stage, if only slightly advanced, may undoubtedly pass off. The degenerate cells are carried away by the urine; from those which remain in the tubes the fat is probably partially absorbed, the retrograde process gradually ceases, and the organ returns to nearly its normal size and condition. In other cases the degeneration continues, and, owing to the loss of epithelium, the kidney becomes somewhat diminished in size. This atrophy, however, I believe never occurs without changes in the intertubular connective tissue.

When the inflammatory process is of longer duration, or when the kidneys are the seats of repeated attacks of subacute inflammation, *the intertubular connective tissue invariably becomes involved.* This tissue becomes infiltrated with small cells which ultimately tend to form a fibrillated structure (Fig. 139). The new intertubular growth may gradually increase, and so lead to more or less irregular atrophy of the organ, such as will be described as occurring in interstitial nephritis. (See "Interstitial Nephritis.") In other cases death

FIG. 139.



Tubal Nephritis. Duration of disease, six months. Kidneys large; capsules non-adherent; surface smooth; tissue soft; showing, in addition to the intratubular change, the cellular infiltration of the intertubular connective tissue. × 200.

ensues before any marked atrophy has taken place, and thus the organ may remain smooth and large to the termination of the disease. The intertubular growth is sometimes found thickly studded with fatty granules.

SCARLATINAL NEPHRITIS.—The changes which take place in the kidney in scarlatina were formerly regarded as precisely similar to those which have been just described as tubal nephritis. Recent investigations, however, show that this view requires considerable modification. It has long been known that in scarlatina cases sometimes occur in which the kidney-change differs from the type of ordinary acute nephritis; and such cases have been described by Prof. Klebs as **glomerulo-nephritis.** It is mainly, however, owing to the more recent researches of Dr. Klein that any exact knowledge of the scarlatinal kidney exists.[1] The changes as described by Dr. Klein may be thus briefly summarized:

The earliest changes, those occurring during the first week of the disease, comprise—

1. Increase of the nuclei covering the glomeruli of the Malpighian corpuscles.

2. Hyaline degeneration of the elastic intima of minute arteries, especially of the afferent arterioles of the Malpighian corpuscles. This change produces a swelling of the intima, so as in some places to cause a distinct narrowing of the lumen of the vessel. The capillaries of the Malpighian corpuscles are in parts altered in the same way, in consequence of which many of them become impermeable.

These marked and early changes in the Malpighian corpuscles are important, as helping to explain those cases occasionally met with in which death occurs from anuria and uræmia, and no catarrhal or other conspicuous alterations are found in the kidneys.

3. Multiplication of the nuclei of the muscular coat of the minute arteries, and a corresponding increase in the thickness of the walls of these vessels.

4. Cloudy swelling of the epithelium in the convoluted tubes, with multiplication of the epithelial nuclei. Granular matter, and even blood, may also be found in the tubes and in the cavity of Bowman's capsules. These parenchymatous changes are in the early stages of the disease but little marked.

The later changes, those occurring after the first week, consist in—

5. A cellular infiltration of the intertubular connective tissue of the cortex (interstitial nephritis), together with an increase in the

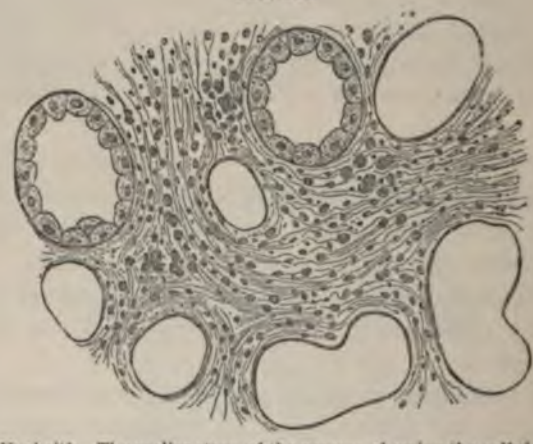
[1] "The Anatomical Changes of the Kidney and other Organs in Scarlatina of Man," by Dr. Klein, *Trans. Path. Soc. Lond.*, 1877, vol. xxviii.

epithelial changes and a crowding of the tubes with small round cells (leucocytes). The cellular infiltration commences around the larger vascular trunks, whence it spreads rapidly into the bases of the pyramids, and especially into the cortex. As it increases the epithelium undergoes fatty degeneration and the urine-tubes gradually become obliterated.

Interstitial Nephritis.

Interstitial or chronic nephritis is characterized by a gradual increase of the connective tissue of the kidney and by atrophy of the tubular structures. This, as has been seen, occurs in the more advanced stages of tubal nephritis (see Fig. 139), in scarlatinal nephritis, and also as a result of obstruction in the lower urinary passages. But it is most frequent, and constitutes the most prominent structural change, in that most chronic variety of Bright's disease which is known as chronic Bright's disease with contracted kid-

Fig. 140.



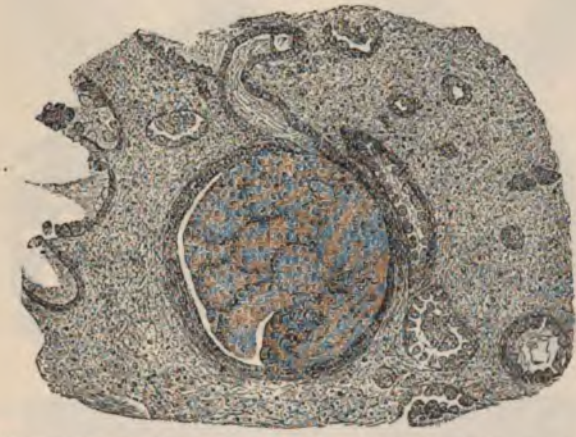
Interstitial Nephritis. The earlier stage of the process, showing the cellular infiltration of the intertubular connective tissue. The epithelium has fallen out of some of the tubes during the preparation of the section. × 200.

ney, and which is characterized clinically by insidious onset, increased secretion of urine, with the absence both of marked albuminuria and of dropsy. It must, however, be directly understood that no line of demarcation is to be drawn histologically between *inter-* and *intra-* tubular changes, or clinically between the two varieties of Bright's disease. Intertubular changes are most marked as the result of

long-continued irritation, and they therefore constitute the prominent histological feature in the most chronic forms of this disease.

In these most chronic cases the changes in the kidneys, being so exceedingly gradual in their onset, are not preceded by any marked vascular phenomena or by any alterations in the tubular epithelium. The first change appears to consist in some cellular infiltration of the intertubular connective tissue (Fig. 139); but usually, owing to the chronicity of the process, the cells are not numerous. The cortical

FIG. 141.



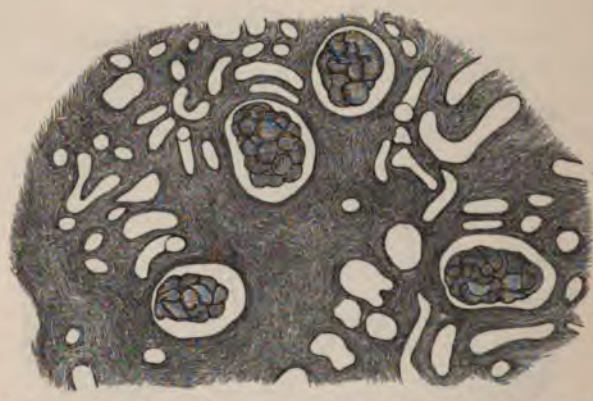
Interstitial Nephritis. An advanced stage of the process, showing the intertubular tissue, with the granular and fatty débris which result from the degeneration. × 100.

portion of the kidney is principally involved, and although here the change is more or less general, the new growth is more abundant in some parts than in others, being usually most so around the Malpighian bodies and in the neighborhood of the capsule, with which it is closely united. In this stage the tubes and their epithelium are often unaffected.

In the early stage the kidney may be of natural size, the capsule usually separates less readily than in health, and the surface of the organ is slightly granular. On section, the cortical substance is in some cases paler, in others redder, than natural. The cut surface also looks obscurely granular, and the consistence of the kidney is usually slightly dense and tough. As the process advances the tubular structures gradually atrophy. This is probably mainly owing to the pressure exercised by the intertubular growth and to the cicatricial contraction which it undergoes. The atrophy consequent-

ly is not uniform, but is more marked in some parts than in others. The tubes are now found in many parts diminished in size or completely obliterated, whilst in others they are irregularly dilated and filled with degenerate epithelial products. Their walls are usually thickened. As the atrophy proceeds, the intertubular tissue thus becomes mingled with the granular and fatty débris which results from the retrograde process (Fig. 141). The Malpighian bodies become approximated and the secreting structure throughout large

FIG. 142.



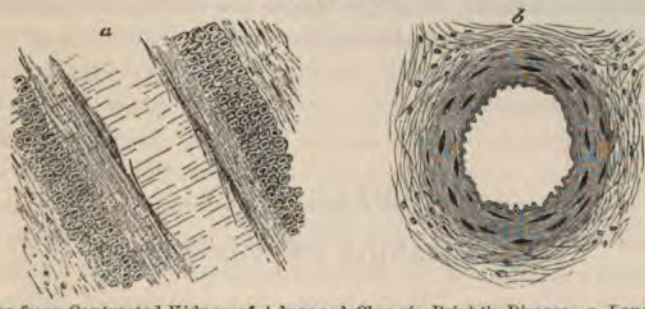
Interstitial Nephritis. A very advanced stage of the process, showing the large amount of tissue between the tubes of the cortex and the extensive atrophy of the tubes. The degenerate epithelium which was contained in some of the tubes has fallen out in the preparation of the section. × 150.

tracts of the kidney is destroyed (Fig. 142). The irregular pressure exercised by the new growth gives rise also to the formation of cysts. These originate partly in the Malpighian capsules and partly in the urine-tubes, the latter becoming irregularly dilated.

The small arteries of the kidney also undergo important alterations. These were first described by Dr. Johnson. Dr. Johnson states that the walls of these vessels are thickened, owing to hypertrophy of their circular muscular fibres; this change is well represented in the accompanying drawing (Fig. 143). The external fibrous coat of the vessel is also thickened, and it appears to be continuous with the new intertubular tissue. This thickening of the external coat has been specially insisted upon by Sir W. Gull and Dr. Sutton. I have usually found it associated with the muscular hypertrophy which is undoubtedly the most prominent structural change. Similar changes occur in the vessels of other parts.

Sometimes the intima is the coat chiefly affected, as shown in Fig. 144; in these cases Dr. F. W. Mott believes that a history of syphilis, as well as of chronic Bright's disease, will be discoverable.

FIG. 143.



Arteries from Contracted Kidney of Advanced Chronic Bright's Disease: *a*. Longitudinal section, showing the great thickening of the circular muscular coat, also of the outer fibrous coat and the internal connective-tissue layer. *b*. Transverse section of another vessel less diseased. Here is seen the thickening of the circular muscular and external fibrous coat. × 200.

In this more advanced stage of the disease the kidney is diminished in size. Its surface is more granular, the capsule more thickened and adherent, and it cannot be removed without tearing the kidney

FIG. 144.

An Acutely Congested Kidney in a Case of Chronic Interstitial Nephritis, in which there was a History of Syphilis. The artery cut across has its lumen diminished by thickening of its intima.

substance. The superficial vessels are seen unduly marked in the depressions between the granulations. The cortex is tough and fibrous, of a reddish, yellowish-gray or buff color, mottled with yellow streaks and patches; and usually numerous small cysts are distributed throughout it. Calcareous deposits also are sometimes seen as white streaks between the tubes of the pyramids.

CHAPTER XLIV.

INFLAMMATION OF THE LUNGS.

In the lungs inflammatory processes comprise the three following principal varieties: **croupous, broncho-** or **catarrhal,** and **chronic** or **interstitial** pneumonia. Of these, the former occurs as an independent affection, whereas the two latter are usually the result of some antecedent bronchial or pulmonary inflammation.

Acute, Croupous, or Lobar Pneumonia.

Acute pneumonia is an inflammation of the parenchyma of the lung, leading to the solidification of a considerable area of the organ—upon one side only, as a rule, and usually the right. The irritant seems to reach the lung from the blood—at least the morbid anatomy lends no support to extension of the inflammation by the bronchi—and to cause an inflammation which extends by continuity of tissue from the primary focus. This in the great majority of cases is in the lower lobe—usually its lower part, whence spread upward occurs—but the disease may begin at any point and extend in any direction, the higher points of the lung being rarer than the lower. A lobe may be accurately mapped out ("lobar"), but often its limits are not reached, or, again, they are overstepped.

The lung inflammation is always accompanied by inflammation of the pleura over the inflamed area, and sometimes the infection spreads to the peritoneum and pericardium; the bronchial glands are inflamed and swollen: occasionally, too, acute secondary meningitis arises in the course of the disease, the etiology being as yet unknown. The disease is accompanied by high fever, of which it is uncertain whether it is primary or secondary, beginning usually with a sudden rise and

marked initial symptoms and ending by crisis; cloudy swelling of organs results. Death when it occurs seems to be due to cardiac failure induced by general poisoning.

ETIOLOGY.—This disease was formerly attributed to the action of cold, to a "chill," and in certain cases the origin of the disease in connection with exposure to cold and damp is very striking. It is, however, impossible, even in these instances, to regard cold as more than a predisposing cause, for exposure to cold is alleged as a cause in only a small minority of the cases. Moreover, it is said to be only slightly more common in men than in women, and not to specially affect those classes of men who are much exposed to vicissitudes of weather. Lastly, pneumonia cannot be produced by exposure to cold or by the infliction upon the lung of a mechanical or chemical injury. Similarly, depressed health is only a predisposing cause, typically healthy people being not uncommonly affected, and sometimes with a fatal result. Again, when compared with a cold-weather disease like bronchitis, pneumonia is found to reach its maximum and minimum at different times from bronchitis.

In the present state of our knowledge we should naturally expect to find the cause of a disease such as pneumonia in an organism, especially when we know that, whilst there is not the least evidence of contagiousness, in some years it is so prevalent as to be practically epidemic, that small outbreaks occasionally occur in wards, prisons, etc., and that it is sometimes endemic in a house, attacking different people in it from time to time. Various observers have described organisms as characteristic of the disease, but none has yet been proved to bear a causal relationship to it. (See chapter on "Vegetable Parasites.") It is doubtful whether all cases of primary acute pneumonia are due to one and the same parasite (Weichselbaum); and it is still more doubtful whether secondary acute pneumonia, arising in the course of such diseases as typhoid or erysipelas, always owes its origin to the same organism.

The disease is variably regarded as an infective inflammation of the lung, as erysipelas is of the skin—the fever being secondary to the inflammation and due to the passage into the blood of pyrogenous ferments—or as a general infective disease (an acute specific fever), of which the lung-inflammation is the characteristic local lesion, analogous to the rash and throat of scarlatina. The "typical" course of the fever, ending usually in a crisis between the fifth and eighth days,

and the absence of any constant relation between the extent of the local inflammation and the intensity of the fever, are generally regarded as being in favor of the latter view. The essential difference between the two views would seem to be that the blood is infected from the lung according to the first, whilst in the second the irritant reaches the lung from the blood, having entered perhaps through the alimentary mucosa.

Pneumonia is often recurrent in a person who has once suffered from it.

MORBID ANATOMY.—The local process is characterized by intense inflammatory hyperæmia of the lung, and by the exudation of a large amount of coagulable material into the pulmonary tissue. It is termed "croupous" by the Germans, from the supposed resemblance of the histological process to that of croup. The term "lobar" is applied to it because it almost invariably affects an extensive portion of the lung. The process is commonly described as consisting of three stages: 1st, that of **engorgement**; 2d, that of **red hepatization**; and 3d, that of **gray hepatization.**

In the *first* stage, that of **engorgement**, the lung becomes exceedingly vascular, the changes in the blood-vessels and circulation being such as have been already described as characteristic of inflammation. The organ is of a dark-red color, its specific gravity and absolute weight are increased, its elasticity is diminished, it is less crepitant and more friable than natural, and pits upon pressure. Its cut surface yields a reddish, frothy, tenacious liquid.

In the *second* stage, that of **red hepatization**, there is an exudation of liquor sanguinis and migration of blood-corpuscles into the pulmonary tissue. Some of the vessels may also rupture, and thus small extravasations occur. The exuded liquids coagulate within the air-vesicles and terminal bronchioles, the coagulum enclosing numerous white and some red blood-corpuscles, the lung-tissue being exceptionally rich in capillaries (p. 248) (Fig. 145). It is stated by some German pathologists that the coagulum is in part produced by certain changes in the epithelium, like those believed to occur in croup (p. 271). The lung is now much heavier than in the preceding stage, and is increased in size, so as to be often marked by the ribs. The pleura over the inflamed lobe is covered with lymph and bulged out by swelling of the lung beneath, the dark purple color of which is visible through. It is quite solid, sinks in water, and cannot be arti-

ficially inflated. It does not crepitate under the fingers, and is remarkably friable, breaking down readily with a soft granular fracture. The cut surface has a markedly granular appearance, seen especially when the tissue is torn. This is owing to the plugs of coagulated exudation-matter which fill the alveoli projecting from them. There is no lobulation of the margin of the inflamed area, no outlying racemose nodules or other indication of infection spreading by the bronchi. The color is of a dark reddish-brown, often

FIG. 145.

Croupous Pneumonia. Red hepatization, showing the fibrinous coagulum in one of the pulmonary alveoli, enclosing within its meshes numerous leucocytes, which are already commencing to undergo fatty metamorphosis. A few leucocytes are seen also on the alveolar walls, and the alveolar epithelium is swollen and granular. × 200.

here and there passing into gray. This admixture with gray sometimes gives a marbled appearance. The red color is due chiefly to vascular engorgement, but partly to extravasated red corpuscles. Throughout this stage there appears to be but little alteration either in the alveolar walls or in the alveolar epithelium. On the former are often

seen a few leucocytes, and the latter is usually swollen and granular (Fig. 145). The pleura covering the solid lung always participates more or less in the inflammatory process. It is opaque, hyperæmic, and coated with lymph.

FIG. 146.

Croupous Pneumonia. Gray hepatization, showing the large accumulation of cellular elements within one of the pulmonary alveoli, which in some parts have undergone such extensive fatty degeneration that their distinctive outlines are no longer visible. × 200.

The third stage, that of **gray hepatization,** is characterized by a continuance in the emigration of leucocytes and by more marked changes in the epithelium. The white blood-corpuscles continue to escape from the vessels, their number within the alveoli gradually increasing. The epithelial cells lining the alveolar walls become more swollen and granular, and the walls themselves become more or less infiltrated with leucocytes. The walls and the contents of the alveoli now assume a uniform appearance and the granular look of the red stage is lost (Fig. 145). The fibrinous material next disintegrates, and the white cells rapidly undergo fatty changes, whilst the red are decolorized; so that, as usually seen, the alveoli are filled with granular elements which in many parts have lost their distinctive outlines (Fig. 146). Occasionally, when this stage is unusually advanced, the alveolar walls may be found here and there partially destroyed. The weight, density, and friability of the lung now become even greater

than in the stage of red hepatization, although the granular aspect of the cut surface is much less marked. The tissue is now quite soft and pulpy and a puriform liquid exudes from its cut surface. The most prominent feature, however, is the alteration which takes place in the color of the organ. This gradually changes from a dark reddish-brown to a gray or yellowish-white, usually marbled by the now visible pigment-bearing connective-tissue tracts of the lung. The pallor is owing partly to the fatty degeneration which the latter have undergone, and partly to the pressure exercised upon the blood-vessels by the exuded substances and newly-formed cells; but, as Rindfleisch has shown that it is always easy to inject the vessels, it would seem likely that a good deal of the pallor is due to post-mortem expression of blood. The stage of gray hepatization, when far advanced, has been termed "suppuration or purulent infiltration of the lung."

Although these three stages of the pneumonic process have been described as succeeding one another in orderly succession, it must be remembered that each stage does not occur simultaneously throughout the whole of the affected area of the lung. The changes advance irregularly, so that whilst one portion of the lung is in the stage of red hepatization, another may be in the gray stage; hence the mottled, marbled appearance of the consolidation. The rapidity also with which the several stages succeed one another is subject to marked variations. In some cases the pneumonic consolidation very rapidly becomes gray, whilst in others the time occupied in the transition is much longer.

The bronchi of the affected area are always inflamed and contain usually a viscid, blood-stained ("rusty") mucus, which forms the characteristic expectoration. When, as is sometimes the case, the sputum is dark and watery ("prune-juice"), it is probably owing to admixture with œdema-fluid from neighboring parts of the lung (Wilson Fox).

TERMINATIONS.—The pneumonic process may end in four ways:

1st. **In Resolution.**—The gradual return of the lung to its normal condition is the natural, and much the most frequent, termination of croupous pneumonia. This is effected by the fatty and mucoid degeneration of the inflammatory products which have accumulated within the alveoli, which thus become so altered that they can be removed by absorption, together with the return of the blood-vessels

to a normal condition and the establishment of the circulation. Granular pigment, derived from the escaped red corpuscles, is often mixed with the softened matters and appears in the expectoration. It is usually taught that where this process of resolution is taking place in the lung the granular appearance of its cut surface is completely lost; it is of a yellowish-gray color, and a tenacious puriform liquid can be expressed from its substance. But, obviously, we do not know the appearances of cases which recover. The sputum gives no support to the view that resolution takes place by the cell-infiltration and general softening of gray hepatization, and it seems probable that those pathologists are right who hold that advanced gray hepatization is incapable of recovery.

2d. **In Abscess.**—The formation of abscess is a rare result of pneumonia. Such a result appears to be favored by a bad constitution and by any circumstances which tend to impair the general health, especially the abuse of alcohol. The abscess is more common in the upper than in the lower lobes. Circumscribed gangrene of the lung also may occasionally terminate in abscess. This takes place by the expulsion of the necrosed tissue through the bronchi, and the formation of a layer of granulation-tissue upon the walls of the cavity, which generates pus. The cavity may ultimately close by granulation and cicatrization. These abscesses of primary origin are usually single, and thus differ from those due to pyæmia.

3d. **In Gangrene.**—This, which is also rare, is most common in chronic drunkards and in those of debilitated constitution. Two conditions appear to be principally concerned in bringing about this result. One is the interference with the supply of blood by extensive formation of coagula in the pulmonary and bronchial vessels, together with considerable hemorrhage into the pulmonary tissue; the other is the injurious influence of septic inflammatory products. The gangrene is usually limited to a small area of the pneumonic lung, and is either diffuse or circumscribed.

4th. **In Chronic Pneumonia.**—If the inflammatory process does not subside and the exuded substances are not absorbed, the alveolar walls gradually become involved. These become thickened by a new growth of fibro-nucleated tissue, and thus is produced more or less fibroid induration or cirrhosis of the organ. This termination of croupous pneumonia is comparatively rare.

Broncho-Pneumonia, Lobular or Catarrhal Pneumonia.

DEFINITION.—Broncho-pneumonia is an inflammation of the parenchyma of the lung due to an irritant entering and spreading by the bronchi, and generally, but not necessarily, first exciting catarrh of the smaller bronchi, to which the pneumonia is then consecutive.

ETIOLOGY AND VARIETIES.—"Simple" or "non-specific" broncho-pneumonia signifies the extension of "simple" bronchitis to the alveoli, which is so apt to occur in young children and in the aged, and with such a fatal result. We must not, however, attribute this to the mere supervention of inflammatory consolidation of a few small patches of lung-tissue—though this doubtless raises the temperature and increases the dyspnœa—but rather to the pre-existing extension of the bronchitis to the finer tubes, which induces the pneumonia, death being due to exhaustion and asphyxia.

But irritants other than those (not definitely known) of "simple" bronchitis—of which cold is such a strong predisponent as at least *to seem* an excitant—gain access to the lung and excite bronchitis, and, more or less frequently, broncho-pneumonia. Among them we may mention irritant gases; dusts of various kinds, particles of carbon (p. 106), steel, iron, stone, etc., which differ much in their irritant power, and organisms, of which by far the most important is the bacillus of tubercle, for tubercular broncho-pneumonia is *the* lesion of phthisis: among others which may enter the lungs by aspiration we may mention the actinomyces and bacillus of glanders, and apparently also the specific causes of the bronchitis of measles and pertussis.

Lastly, portions of food or saliva, carrying septic germs, may enter (especially after section of the vagus), and blood during operations on mouth, nose, etc., and putrid discharges from diseases or wounds of these parts may be aspirated into the bronchi and give rise to suppurative or gangrenous broncho-pneumonia. Simple bronchitis and the specific forms due to infection of the tubes and alveoli by the irritants of measles, whooping cough, variola, diphtheria, and tubercle are by far the commonest varieties of broncho-pneumonia. Tubercular broncho-pneumonia frequently affords an instance of the occurrence of the pneumonia without any bronchitis—sufficient to attract attention, at all events, though signs of bronchitis at the apices are often some of the earliest indications of tubercle: it affords also a frequent exception to the rule that, being consecutive to bronchitis, broncho-pneumonia affects both lungs.

All conditions depressing the general health and strength predispose to broncho-pneumonia—1st, by weakening the resistance of the tissues and favoring their infection and the spread of an inflammation; and 2d, it is said, by diminishing the power of the respiratory muscles, and thus aiding the occurrence of pulmonary collapse from occlusion of the finer tubes by swelling of the mucous membrane and catarrhal secretion. Collapse certainly seems frequently to precede the inflammation, but proof of its importance as a predisponent to broncho-pneumonia does not seem to be forthcoming: it may, by throwing them out of function, still further weaken the resistance of the tissues and render infection of the alveoli more easy; but when and where bronchitis has reached the finest tubes extension to the alveoli would seem almost natural without assistance from collapse, such spread being probably assisted by aspiration of the causes of the bronchitis into the alveoli.

PATHOLOGY.—Broncho-pneumonia has been studied experimentally by causing animals to inhale irritant gases or particles suspended in fluids, and by dividing the vagus, after which saliva and food-particles enter the air-passages. The resulting changes vary (1) with the size of the inhaled particles, and (2) with the intensity of the irritation they are capable of exciting. Very fine particles cause widely-scattered miliary foci of inflammation; larger ones block the smaller bronchi, cause collapse and secondary inflammation of lobules, which, being the commonest result, gives the name of "lobular" pneumonia to the disease. Lastly, the aspiration of a quantity of septic discharge or other fluid into a bronchus may affect many lobules or even a whole lobe. According to the intensity of the inhaled irritant the result may vary from mere collapse, accompanied by slight inflammatory œdema, through all stages of inflammation up to gangrene. In the tubercular form, which will be considered under "Phthisis," the inflammatory products caseate.

MORBID ANATOMY.—From the above it will be seen that the appearances of the lungs after death vary much. The bronchi are always more or less inflamed and contain thick mucus. Ordinarily, the lung-tissue exhibits, in varying numbers, solid patches, due either to collapse or to inflammatory consolidation, emphysema of the air-containing tissue round about these, with more or less congestion and œdema. Patches of collapse are most common in the lower lobe,

especially along its thin border: quite a large portion of a lobe may thus be involved or small isolated patches. Collapsed lung is sunk below the lung-surface, has a dark bluish color, is solid, non-crepitant, sinks in water, and is easily inflated from the bronchi; on section it is dark red, smooth, shiny, and the tissue has a clear look. The smaller patches are more or less conical, with their bases toward the surface of the lung and their apices toward the bronchi with which they are in connection. The pleura over a patch of collapse is normal. On the other hand, a pneumonic patch feels much more like a firm nodule in the substance of the lung than does a patch of collapse: when of small size it also is more or less conical, being due to distension of the infundibula of a bronchus; the base tends to project convexly above the surrounding surface, and the pleura is usually unaffected over it, though it may be covered with lymph, especially when a large area is involved. On section the patches may be distinctly outlined or ill defined, and usually range in size from a small pea to a hazel-nut: the surface of section tends to rise slightly above the surrounding tissue; it is friable, soft, opaque-looking, smooth or faintly granular, at first dark red in color, then passing through grayish red to grayish yellow, the lighter color being central. A turbid red or grayish juice can be pressed from it. Neighboring lobular patches tend to blend, and the more diffuse consolidation becomes paler, firmer, drier, and somewhat resembles in appearance ordinary gray hepatization. Sometimes patches of collapse are found becoming swollen, opaque, and œdematous: into these the pneumonic process is spreading.

When broncho-pneumonia is so extensive that the consolidation is "lobar," it is difficult to distinguish from acute pneumonia: evidence of the blending of lobular masses, and especially the presence of outlying nodules in the neighborhood of the main mass, are the most important points to look for. Absence of lymph from the pleural surface is against acute pneumonia, but lymph may form over a broncho-pneumonic area.

In cases of septic broncho-pneumonia—the commonest cause of death after operations on the jaws, mouth, and pharynx—instead of the above solid patches we find abscesses, often containing sloughs of lung-tissue and sometimes fetid: these are surrounded by more or less extensive consolidation, and inflammatory hyperæmia and œdema of the lung are marked.

Microscopically, in the early red stage the alveoli contain fluid, more or fewer red corpuscles, and a few leucocytes, and the alveolar

epithelium is swollen and granular: this latter change, according to Friedländer, is due merely to imbibition, and does not indicate any activity on the part of the epithelial cells. Next, the alveoli become

FIG. 147.

Broncho-Pneumonia, from a child aged four with capillary bronchitis. A section of one of the patches of consolidation, showing the stuffing of the alveoli with what appears in the main to be inhaled bronchial secretion. × 200.

filled with a cell-mass consisting of leucocytes and cast-off epithelium in varying proportions, leucocytes being in excess in the more acute (Fig. 147), the epithelial cells in the more chronic (Fig. 148). In

FIG. 148.

Catarrhal Pneumonia, from a Case of Acute Phthisis, showing the large epithelial cells which fill the alveoli. × 200.

the most acute cases (septic broncho-pneumonia), suppuration and sloughing occur or a hemorrrhagic exudation precedes gangrene.

TERMINATIONS.—Resolution is the most common termination. The contents of the alveoli undergo fatty metamorphosis, and are

removed by expectoration and absorption, the lung gradually regaining its normal character. This process, however, is less readily affected than in croupous pneumonia, and it often occupies such a lengthened period that some thickening of the bronchial and alveolar walls and dilatation of the smaller bronchi remain. In chronic cases this **fibroid thickening** is much more marked, and considerable irregularly-distributed pigmented induration and bronchial dilatation may be produced (p. 425). In these chronic forms **caseation** sometimes affects the contents of the alveoli, which then become encapsuled, or in quite exceptional cases disintegrate; but, unless the contrary is demonstrated, we should be strongly inclined to regard all such cases as tubercular.

HYPOSTATIC PNEUMONIA.—Allusion must be made here to a form of lung-consolidation which is often described as pneumonic, but which, in reality, is for the most part non-inflammatory in its nature. This is the so-called hypostatic pneumonia. This condition is met with at the bases and most dependent portions of the lungs in the course of both chronic and acute diseases, and also in the aged and debilitated. It consists in the main of collapse, mechanical hyperæmia, and œdema of the lung-tissue, resulting from weak inspiratory power, feeble circulation, and gravitation. The consolidation thus mechanically induced is increased by more or less exudation of liquor sanguinis and blood-corpuscles into the alveoli; which exudation is due to the damage to the walls of the capillaries caused by the imperfect circulation.

Interstitial or Chronic Pneumonia.

Interstitial or chronic pneumonia is characterized by a gradual increase in the connective tissue of the lung, which leads to an induration of the pulmonary texture and to progressive obliteration of the alveolar cavities. It is commonly associated with catarrh and dilatation of the bronchi, and often with ulceration of the bronchial walls and excavation of the indurated lung.

ETIOLOGY.—It is very doubtful if interstitial pneumonia is ever a primary and independent affection. It almost always results from some more acute inflammation of the inner surface of the lung (bronchi and alveoli) or of the outer surface (pleura): it results also from persistent

atelectasis or collapse. It may be stated generally that all inflammatory processes in the lung when they become chronic tend to cause increase of the connective tissue, and consequently fibroid induration of the organs.

Syphilis certainly gives rise to a gummatous and, it is said, also to a diffuse interstitial, pneumonia in children suffering from the congenital form of the disease: of the latter variety very little is known. In adults syphilis of the lung is believed to be rare, but it is very difficult to recognize syphilitic lesions with certainty.

We shall not include under the head of interstitial pneumonia that general fibrosis of the lung which we have already described as "Brown Induration" (p. 212). The chief **causes** of this morbid condition will be—

1. **Croupous Pneumonia.**—The consolidation of acute croupous pneumonia almost always undergoes complete resolution rapidly, but occasionally it is more protracted. Then the hepatized lung tends to become slightly indurated, owing mainly to the thickening of the walls of the alveoli. This indurated hepatization differs but little in its physical characters from ordinary red and gray hepatization: it is simply somewhat firmer, more resistant, and less granular. In very exceptional cases this small amount of induration, commencing in the alveolar walls, may gradually increase, so as ultimately to give rise to that extensive fibrosis of the lung which constitutes what is usually known as interstitial pneumonia.

2. **Broncho-Pneumonia.**—This is a somewhat more frequent cause than the preceding. The greater liability of this form of pneumonia to lead to pulmonary induration is to be accounted for partly by its longer duration and greater tendency to become chronic, and partly by the existence of bronchial dilatation with which it is so frequently associated. That bronchial dilatation is favorable to an indurative pneumonic process has been insisted upon by Dr. Wilson Fox.[1] The existence of this dilatation favors the persistence of the catarrhal and pneumonic process. The removal of secretion is rendered difficult, and the retained secretion tends to keep up and increase the irritative process both in the dilated bronchi and also in the pulmonary alveoli; and this persistence of the bronchial and pulmonary inflammation leads to fibroid thickening of the bronchial and alveolar walls. In this way areas of fibroid induration are produced which, as the process extends, may ultimately involve large portions of the lung. The

[1] "Chronic Pneumonia," in Reynolds' *System of Medicine*, vol. iii.

progressive tendency of the process is probably partly to be explained by the fact that pulmonary fibrosis is a cause of bronchial dilatation, so that fibrosis, once established, by inducing further dilatation of the bronchi favors the extension of the bronchial and pulmonary induration (Wilson Fox).

Under this head may be included also those cases of induration and ulceration of the lung which result from obstruction of a main bronchus, such as is produced by the pressure of an aneurism. Here the retained bronchial secretion sets up inflammatory changes in the bronchial and alveolar walls, which gradually lead to induration and ulceration of the lung.[1]

3. **The Inhalation of Solid Irritating Particles.**—This, which occurs in miners, potters, stonemasons, grinders, etc., is the cause of the fibrosis of the lung so common amongst these workmen. The continuous irritation of the inhaled particles induces a bronchial and alveolar inflammation, and ultimately a progressive fibrosis, with dilatation and ulceration of the bronchi. Such cases often become tuberculous.

4. **Pleurisy.**—This in exceptional cases leads to the development of an interstitial pneumonia. It appears to be in those cases of pleurisy which are more or less chronic, and in which the effusion remains long unabsorbed, that such a result is most liable to occur. The induration of the lung thus induced is often, however, partial, consisting merely in some increase of the interlobular connective tissue, originating and extending inward as dense bands from the thickened visceral pleura. In other cases pleurisy gives rise to a much more general fibrosis.

5. **Atelectasis**—or failure of part of the lung to expand after birth—and *persistent collapse* lead to marked cirrhosis of the area, bronchiectasis, and ultimate obliteration of most of the alveoli, the positions of which are indicated only by a few epithelial cells.

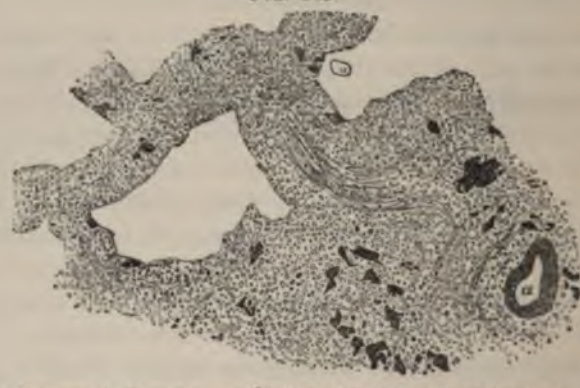
MORBID ANATOMY.—The appearances presented by the lung when the fibrosis is extensive and general are very characteristic. The organ is diminished in size; the tissue is smooth, dense, firm, in parts almost cartilaginous in consistence, and it is irregularly mottled with black pigment. The alveolar structure of the lung is in most parts completely destroyed, and on section the dilated bronchi are seen as numerous large openings scattered over its surface. The

[1] See case by Dr. Irvine, *Trans. Path. Soc. Lond.*, vol. xxviii. p. 63.

dilated bronchi frequently become the seats of secondary inflammatory processes, which may lead to ulceration, and ultimately to extensive excavation of the indurated tissue; but there is a complete absence of any of those caseous changes which are so characteristic of phthisis. This secondary inflammation of the dilated bronchi is induced by irritating and often putrid secretion which they contain, and which is only with great difficulty completely removed by expectoration. The pleura is almost invariably considerably thickened and adherent.

Microscopically, we find development of a fibro-nucleated tissue in the walls of the alveoli, in those of the bronchi, and from the interlobular connective tissue; which new growth, as it increases and contracts, gradually replaces and obliterates the alveolar structure. The character of these changes, however, varies somewhat according to the more acute inflammatory antecedents in which they originate. When the result of a croupous pneumonia, the primary, and usually the principal, change takes place in the walls of the alveoli (Fig. 149),

FIG. 149.



Interstitial Pneumonia, from a case of unilateral "cirrhosis" of the lung. The bronchi were much dilated, and there was a complete absence of any caseous change. The drawing shows the new fibro-nucleated growth, both in the alveolar walls and in the interlobular tissue, also the pigmentation. At *a* a divided vessel is seen. With a higher power a delicate reticulum can be seen between the cell-elements. × 100.

although ultimately the interlobular tissue is involved. The alveolar walls become thickened by the growth of a small-celled tissue, which presents all the appearances found in embryonic tissue which is undergoing fibroid development. The new growth in its earlier stages contains new blood-vessels, but later the tissue contracts and many of these are destroyed. The alveolar cavities which are not obliterated

are either empty or contain exudation-products or a few epithelial cells. In addition to the growth in the alveolar walls, I have met with three cases in which intra-alveolar exudation-products were undergoing fibroid development.[1] There was nothing peculiar in the macroscopical characters of the lungs, but the alveoli were found filled with a fibrinous meshwork and leucocytes somewhat similar to that

FIG. 150.

Chronic Pneumonia. Vascularization and fibroid development of intra-alveolar exudation-products. Blood-vessels are seen distributed in the exudation-products, which blood-vessels communicate with those in the alveolar walls. The alveolar walls are also thickened by a fibro-nucleated growth. × 100, and reduced ½.

met with in red hepatization (Fig. 150). They differed, however, in this respect—that many of the cells were long and spindle-shaped, and

FIG. 151.

Chronic Pneumonia. A portion of the intra-alveolar exudation-products (Fig. 150), more highly magnified, showing the elongated spindle-cells, the fibrillation, and blood-vessels containing blood-corpuscles. × 200.

blood-vessels were distributed amongst them, which blood-vessels communicated with those in the alveolar walls (Figs. 150 and 151). The

[1] For one of these specimens I am indebted to Dr. Goodhart, who records the case in the *Trans. Path. Soc. Lond.*, vol. xxv. p. 33.

alveolar walls also were thickened by a fibro-nucleated growth. It was therefore perfectly obvious that in these lungs the products of a previously acute croupous pneumonia were becoming vascularized and undergoing development into a fibroid structure, and that this intra-alveolar change was the principal cause of the fibroid induration of the organs.

When the fibrosis is secondary to an ordinary broncho-pneumonia or to that induced by the inhalation of irritating solid particles, the new growth also originates principally from the alveolar walls. Here, however, the growth in the earlier stages is less uniform, and the peribronchial and interlobular connective tissue plays a more prominent part in the process (Fig. 152).

FIG. 152.

Chronic Bronchitis, showing the new growth of fibro-nucleated tissue around the bronchus, *b*, and the way in which this tissue is invading the walls of the adjacent alveoli. *v*. A divided blood-vessel. × 100, reduced ½.

The pleurogenous form results chiefly from empyemata. Here the new fibrous tissue extends inward in bands along the interlobular lymphatic vessels, which communicate freely with those of the thickened pleura; thence it spreads to the peribronchial tissue. The lung is thus surrounded by a dense capsule, and a meshwork of anastomosing fibrous bands permeates its substance, compresses the alveoli, and deforms the bronchi. More or less bronchitis is usually present.

Atelectasis and collapse are said to lead first to slight hemorrhages, and the hæmoglobin furnishes some of the black pigment usually found in fibroid areas owning this origin. The alveolar walls become fibroid, the epithelium is more or less shed, and the surfaces of the walls cohere.

CHAPTER XLV.

PULMONARY PHTHISIS.

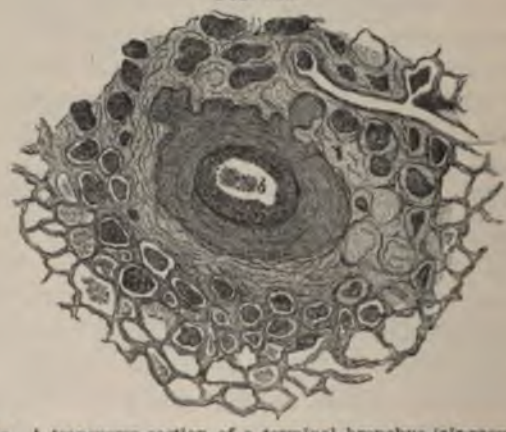
By **Pulmonary Phthisis** is understood a disease of the lungs which is characterized by progressive consolidation of the pulmonary texture and by the subsequent softening and disintegration of much of the consolidated tissue, the upper portions of the organs being in almost all cases the first to become involved.

Respecting the nature of the morbid processes which lead to this consolidation and disintegration of the lungs, various opinions have from time to time been held by pathologists, and this diversity of opinion exists to some—we believe rapidly diminishing—extent even at the present day. According to the older views, which were based upon the teaching of Laennec, phthisis was regarded in all cases as a **tuberculous** disease. Tubercle was looked upon as a non-inflammatory growth which was characterized by the caseous degeneration which it invariably underwent, and this caseous metamorphosis was held to be such a distinguishing peculiarity of the growth that all caseous masses came to be regarded as tuberculous, and phthisis, in which caseation plays such a prominent part, was consequently regarded as a tuberculous disease. The various consolidations of the pulmonary tissue were described as "infiltrated tubercle," and tubercle in some form or other was regarded as so essential a constituent of the disease that "phthisis" and "pulmonary tuberculosis" came to be synonymous terms. When the application of the term "tubercle" became limited by Virchow and his followers to the "gray granulation," it was evident that these views were no longer tenable, and many, in accordance with the advocacy of the late Professor Niemeyer, regarded phthisis as due to a form of caseous pneumonia which was quite independent of tubercle, although this growth might occur as a secondary and accidental complication. It was then said that some cases of phthisis were tubercular, and that others were not, and attempts were made to subdivide the disease into distinct pathological varieties based upon fine and coarse morbid anatomy, such as "tuberculous," "pneumonic," and "fibroid" phthisis. Our present knowledge of tuberculosis, and especially of its etiology, necessarily

involves considerable modification of these older views. Before considering the pathology, however, it will be well to study the histology of the disease.

HISTOLOGY.—The histological changes in the lungs which occur in pulmonary phthisis are similar to those which are met with in these organs in acute miliary tuberculosis. They differ mainly in this respect—that whilst in the latter disease these changes are usually limited to small areas (being due to the distribution of bacilli by the blood and to their deposit here and there in the pulmonary tissue, whence the *miliary* character of the lesions), in the former they usually ultimately involve much wider tracts of tissue. Further, phthisical consolidation is **lobulated** in its distribution, owing to the fact that the injury causing the inflammation is inflicted chiefly through the medium of the bronchi. (See "Etiology.") This lobulated distribution of the consolidation is exceedingly characteristic, and even in those acute cases in which, owing to the rapid and extensive implication of the lung, the consolidation may to the naked eye appear almost uniform (like croupous pneumonia), the microscope will usually reveal a lobular character (Fig. 153).

FIG. 153.



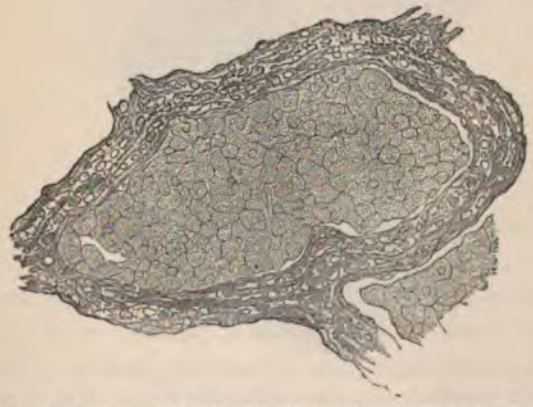
Acute Phthisis. A transverse section of a terminal bronchus (air-passage) and the surrounding alveoli, showing the *lobulated* character of the pulmonary consolidation. *b*, Cavity of bronchus containing a little mucus. × 50, reduced ½.

The structural changes met with in the lungs in phthisis are mainly of four kinds: 1st, an accumulation of epithelial cells within the pulmonary alveoli; 2d, the presence within the alveoli of a fibrinous

exudation and leucocytes; 3d, a cellular infiltration and thickening of the alveolar walls, together with, in most cases, a similar change in the walls of the terminal bronchioles; and 4th, an increase in the interlobular connective tissue. These four kinds of morbid change are very constantly associated, although in very different degrees, and some of them are more prominent and characteristic than others. The preponderance of one or other of them produces those variations in the physical characters of the lungs which are met with in the different stages and in the different varieties of disease. These various structural changes must now be considered separately, together with the more important alterations in the physical characters of the organs which they respectively produce.

1st. **An Accumulation of Epithelial Cells within the Pulmonary Alveoli.**—This is one of the most frequent changes met with in phthisis, and is precisely similar to that which has been already described as occurring in cases of catarrhal pneumonia (Fig. 148). The alveoli are found filled with large nucleated elements, apparently the offspring of the epithelial cells normally lining the alveolar walls (Fig. 154). In some acute cases of phthisis this alveolar accumula-

Fig. 154.



Acute Phthisis, showing one of the alveoli filled with epithelial elements, and marked cell-infiltration of the alveolar wall. × 200.

tion may constitute almost the only morbid change, and, although there is always some cell-infiltration of the alveolar walls, the great bulk of the pulmonary consolidation is due to the stuffing of the alveolar cavities with catarrhal products (Fig. 155). In some parts —those in which the change is the most recent—the large cells

which fill the alveoli and the alveolar walls will be found but little altered, but in the greater portion of the consolidated tissue the cells will be seen in various stages of retrogressive metamorphosis and the alveolar walls destroyed, whilst in those tracts of tissue in which the process is most advanced all trace of structure is lost and nothing is seen but a granular débris. These changes are precisely analogous to those met with in many of the larger nodular lesions of acute tuberculosis (Figs. 98 and 99).

2d. **The Presence within the Alveoli of a Fibrinous Exudation and Leucocytes.**—This is less frequent than the preceding (Fig. 156). The exudation-products are similar to those which fill the alveoli in ordinary croupous pneumonia (Fig. 145). The coagulum, however, is usually not so abundant, neither is the fibrillation quite so distinct. In the most acute forms of phthisis this may constitute the principal cause of the pulmonary consolidation, but commonly it is associated with more or less epithelial proliferation.

The appearances presented by the lungs in those cases in which the

FIG. 155.

Section of Lung from a Case of Acute Phthisis, showing that the consolidation consists almost exclusively of products accumulated within the alveoli. In some parts a free space is seen between the alveolar walls and their contents: this is due simply to the shrinking of the latter caused by the hardening of the specimen. × 50.

pulmonary consolidation is due mainly to the *intra*-alveolar changes above described are very characteristic. The consolidated tissue is quite soft and friable, breaking down very readily under the finger, and there is complete absence of any induration. The consolidation, although sometimes almost uniform, usually presents a somewhat

lobulated outline, indicating the implication of different groups of the pulmonary lobules (p. 421). The color varies from a reddish to a yellowish gray, and scattered through the consolidated mass are often small portions of a more decidedly yellow tint. These latter correspond with those parts in which the retrogressive changes are the most advanced, and they are even softer in consistence than the surrounding tissue. In many parts the consolidated tissue will be found broken-down, so as to form cavities of various sizes. These usually possess irregular walls, which are quite soft and friable like the solid tissue which surrounds them.

3d. **A Cellular Infiltration and Thickening of the Alveolar Walls**, together with, in most cases, a similar change in the walls of

FIG. 156.

Acute Phthisis, showing one of the alveoli filled with fibrinous exudation and leucocytes, and some cellular infiltration of the alveolar wall. × 200.

the terminal bronchioles.—This must be regarded as the most characteristic phthisical lesion, it is so constantly associated with the above intra-alveolar changes, whilst it is only exceptionally present in the more acute pulmonary inflammations; its extent, however, varies very considerably in different cases. The change is precisely similar to that which has been already described as occurring in acute miliary tuberculosis. In its earlier stages a few small lymphoid cells are seen infiltrating the alveolar septa, which are thus slightly thickened (Figs. 154 and 156). As the change proceeds the number of these cells increases, and from them an imperfect fibro-nucleated structure is developed (Fig. 157). This structure contains no new blood-vessels.

As this new tissue develops in the alveolar walls, it gradually obliterates and replaces the alveolar cavities, so that whilst in some portions the thickened alveoli may be found still containing epithelial elements, exudation-products, or even giant-cells, in others large tracts will be

FIG. 157.

Section of Lung from a Case of somewhat Chronic Phthisis, showing the thickening of the alveolar walls by a fibro-nucleated tissue resembling lymphoid tissue, together with an accumulation of epithelial cells within the alveolar cavity; the latter are undergoing retrogressive changes. × 200.

seen consisting almost entirely of the small-celled growth. The development of this new non-vascular tissue in the alveolar walls leads to the partial, or even complete, obliteration of the pulmonary capillaries, which, as will be seen subsequently, constitutes an important element in the causation of the retrograde changes.

The changes which may subsequently take place in this alveolar growth vary. The infiltrated septa may rapidly break down before any marked thickening or development of new tissue has had time to occur, whilst in other less acute cases there is a considerable development of the imperfect fibro-nucleated tissue, which, although it may remain as a more or less permanent structure, usually, owing to insufficient vascular supply—or, more probably, owing to inability to resist the invasion and prevent the growth of the tubercle bacillus—undergoes in its turn retrogressive metamorphosis. These two kinds of change are very often found taking place simultaneously in different portions of the consolidated lung. In those portions in which the new tissue is undergoing degeneration, it, together with the cells which may be contained within the alveoli, will be seen to have become con-

verted into a structureless granular débris, whilst perhaps in the immediate vicinity of these degenerated portions will be found a more permanent fibro-nucleated structure.

Respecting the alteration which the growth of this small-celled tissue produces in the physical characters of the lungs, it may be stated generally that it usually leads to more or less induration of the pulmonary texture. The extent of this induration, however, will vary according to the characters of the new tissue. If the tissue be almost entirely cellular, as is the case when it is very rapidly developed, it will produce but little, if any, induration of the pulmonary consolidation, which, consisting mainly of the intra-alveolar accumulations, will be soft and friable in consistence, much resembling that which has been already described. When, on the other hand, as is more frequently the case, there is any considerable development of the imperfect fibro-nucleated growth or its reticulum is dense and abundant, there will be a corresponding induration of the consolidated tissue. In many cases these changes produce uniform tracts of indurated consolidation of a grayish color mottled with black pigment, in which there may be scattered here and there yellowish patches corresponding to portions which have undergone retrogressive fatty changes.

4th. **An Increase in the Interlobular Connective Tissue.**—This is met with, to a greater or less extent, in all the more *chronic* forms of phthisis. This tissue, which surrounds the bronchi and blood-vessels and contributes to the formation of the alveoli, is found not only increased in amount, but also altered in character. In the earlier stages of its development, when it contains numerous small cells, although many parts of it may resemble the growth in the alveolar walls, its structure is more like that met with as the result of chronic indurative processes in other organs. It has a much greater tendency to become developed into a fibroid tissue than the alveolar growth, and is rarely the seat of those retrograde changes which are so frequent in the tissue originating in the alveolar walls. As usually met with, it consists either of wavy fibres or of a more or less reticulated structure, with a varying number of round, spindle-shaped, or branched cells (Fig. 158). Associated with it in most cases are granules of black pigment. These differences in the pathological tendencies and structure of the alveolar and interlobular growths are mainly owing to differences in the amount of their vascular supply. Whereas in the former the vessels become obliterated in the manner already described, in the latter this obliteration is much less complete or

entirely wanting. In the most chronic cases of phthisis this interlobular growth may constitute the predominant structural change, and large tracts of the pulmonary texture may be found completely replaced by it. (See "Interstitial Pneumonia.")

An increase in the interlobular connective tissue in phthisis, inasmuch as the new tissue has so marked a tendency to become dense

Fig. 158.

Chronic Phthisis, showing the new interlobular fibroid growth surrounding and encapsulating a degenerated and caseous portion of the consolidated lung. × 50, reduced ⅓.

and fibroid, leads to extensive induration of the pulmonary texture; and further, owing to the contraction which the tissue tends to undergo, its growth ultimately produces a corresponding contraction of the diseased lung. In all those cases of phthisis in which there is either a marked thickening of the alveolar walls or an increase in the interlobular connective tissue any cavities which may exist in the consolidated and indurated tissue are characterized by the tough and fibroid character of their walls, these presenting a marked contrast to the soft, friable tissue which surrounds the cavities in cases in which the pulmonary consolidation is due mainly to intra-alveolar change.

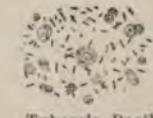
Changes in the Bronchi.—Allusion must now be made to certain changes in the bronchi. These tubes are invariably more or less involved in pulmonary phthisis. Some catarrh of the bronchi is constantly present in phthisical lungs. The catarrh is sometimes general

but much more commonly it is limited, and more strictly confined to such portions of the lung as are becoming, or have already become, consolidated. In many cases there is a marked tendency of this bronchial catarrh to lead to extensive cell-infiltration of the deeper structures of the bronchial wall. This cell-infiltration sometimes leads to the production of small ulcers. These have thickened opaque edges, and when once formed they tend to increase. In addition to these changes in the bronchial mucous membrane there is often a cellular infiltration of the peribronchial tissue, and here small nodules of new growth are frequently met with, especially around the smallest bronchi.

PATHOLOGY.—Having thus briefly described the various structural changes met with in the lungs in phthisis, it remains to consider the nature of the morbid processes upon which they depend. In the first place, it is evident that these changes are structurally analogous to those we have met with in the several forms of pulmonary inflammation. The exudation of fibrin and leucocytes and the accumulation of epithelial cells within the alveoli in croupous and catarrhal pneumonia, with, in the more chronic cases, the ultimate infiltration of the alveolar walls and the increase in the interlobular connective tissue which characterizes the interstitial process, closely resemble the phthisical lesions. These considerations, together with others derived from the study of the etiology of the disease, are sufficient to justify the conclusion that the morbid processes which lead to the consolidation and subsequent disintegration of the lung come within the category of **inflammation**, and that the differences in the histological changes to which they give rise are due mainly to differences in the intensity and duration of the inflammatory process.

But although phthisical consolidation of the lung is the result of inflammation, it is obvious from our previous considerations (p. 274) that the process does not owe its origin to "simple" causes. The *progressive* character of the inflammation and its tendency to infect adjacent and distant portions of the lung show the existence of some constant irritant capable of multiplication in the body and of spreading from a primary to secondary foci; and for some years past the presence of some **pathogenic organism** has become increasingly probable. Koch discovered the organism (p. 311). His and all subsequent investigations tend to show that the Bacillus tuberculosis is invariably present, both in the

FIG. 159.



Tubercle Bacilli in Phthisical Sputum. × 300.

lungs and in the sputum, in all cases of phthisis (Fig. 159); and we must therefore regard phthisis as a more or less chronic **pulmonary tuberculosis**—*i. e.* we have returned to Laennec's view, but, unlike him, regard tubercular lesions as inflammatory.

In considering the causes of the differences in the histological changes in the lungs, it is important to bear in mind what has been already stated respecting the variations in the character of the textural alterations in inflammation which are produced by differences in the intensity and duration of the inflammatory process. When studying the process of inflammation it was seen that the most intense forms of the process were characterized by abundant fluid and corpuscular exudation, whereas in inflammations of less intensity and longer duration tissue-formation played a prominent part. These textural changes also varied according to the duration of the inflammation. In the least severe and most chronic forms these changes tended to be limited to the elements immediately adjacent to the blood-vessels and lymphatics, whereas in inflammations of somewhat greater intensity more distant elements became involved. Further, whereas in the former case these changes usually resulted in the formation of a small-celled tissue which tended to become fibroid, in the latter the more distant elements—being in most cases incapable of further development—tended to undergo retrogressive changes. In the lungs the truth of these propositions was borne out by the differences which were seen to exist in the histological characters of the lesions in the various forms of pulmonary inflammation and also in acute tuberculosis.

If the pathology of these inflammatory processes in the lungs be kept in view, the explanation of the differences in the histological characters of the lesions in pulmonary phthisis becomes evident. In those cases in which the inflammatory processes are of slight intensity and of long duration the most marked structural change will consist in the development of a small-celled growth in the alveolar walls and in the interlobular tissue—a growth which tends more or less to become developed into a fibroid structure; whereas in those cases in which the inflammation is of greater intensity fluid and corpuscular exudation and proliferation of the alveolar epithelium will constitute more prominent parts of the process.

The intensity of the inflammatory process not only determines the histological characters of the pulmonary consolidation, but also, to a great extent, the subsequent changes which take place in it. In those cases of phthisis in which the intensity of the inflammatory process is

considerable, not only do the epithelium and exudation-products which have accumulated within the alveoli quickly degenerate and break down, but any small-celled tissue which may have been developed in the alveolar walls or around the terminal bronchioles also softens and dies, and thus the vitality of large tracts of the pulmonary consolidation may become destroyed. In those cases, on the other hand, in which the process is less intense the small-celled growth produced in the alveolar and bronchial walls is more permanent, and there is an increase in the interlobular connective tissue. It is these two kinds of change—the one tending toward death and the other toward the production of new tissue—which produce the caseation and softening on the one hand and the induration on the other, which, associated in such various degrees, make up the diverse physical characters of the phthisical lung.

These various **secondary changes** which may take place in the pulmonary consolidation of phthisis must be considered more fully. They are of three kinds—resolution, development into an imperfect fibroid tissue, and retrograde metamorphosis.

Resolution.—Much of that consolidation of the lung which is the most rapidly induced, and which is consequently owing to the presence of intra-alveolar exudation-matter, may become absorbed. The resolution of the consolidation may thus be complete, or after the absorption of the intra-alveolar products there may remain more or less infiltration of the alveolar walls.

Fibroid Development.—This, as has been seen, may take place in the growth in the alveolar walls and also in the new interlobular tissue. The tissue which originates in the walls of the alveoli, being for the most part destitute of blood-vessels, is incapable of forming a very mature structure, but it may develop into an imperfect tissue, and remain for some time permanent, thus contributing to the induration of the lung. In the new interlobular tissue there is not the same interference with the vascular supply, and hence this forms a much more fully developed and permanent structure, and is the principal source of the pulmonary fibrosis. The extent of this fibrosis is, for the most part, in direct proportion to the chronicity of the disease.

Retrograde Metamorphosis.—It is this kind of change which leads to that caseation, softening, and disintegration which is so characteristic of phthisis, and which distinguishes phthisical from other forms of pneumonic consolidation. A retrograde change in the

inflammatory products is an invariable accompaniment of acute non-phthisical pneumonia. Much of the exudation-matter and epithelium which fill the alveoli undergoes fatty and mucoid changes, and, as the circulation becomes restored in the pulmonary capillaries, the degenerated products are absorbed and the lung remains intact. In phthisical consolidation, however, the removal of the inflammatory products does not take place. The contents of the alveoli degenerate, but the degenerated products are not absorbed, and the consolidated lung undergoes a rapid or gradual process of disintegration.

In studying the causes of this retrograde metamorphosis, which constitutes so essential a feature of the disease, we find that it has usually been attributed to conditions interfering with the circulation. Of these, that which probably occupies the most prominent place is the cell-infiltration of the walls of the alveoli and smaller bronchi which is such a constant though very variable factor in phthisis. When the infiltration is marked, and especially when rapidly induced, the effect of the pressure which the young cells exercise upon the pulmonary capillaries is to obstruct the circulation, and many or all the vessels soon become obliterated; thus, not only is absorption of any intra-alveolar products prevented, but necrotic changes naturally result. These are cases in which the irritation of the bacilli is great in proportion to the resisting power of the tissues.

Among other conditions tending to interfere with the circulation, and so to cause necrosis, must be mentioned, as obtaining in the most acute forms of phthisis, the pressure exercised upon the pulmonary capillaries by the inflammatory products which have accumulated within the alveoli, and that tendency to stagnation of the blood-stream which is an invariable accompaniment of every intense inflammation.

But these are obviously not *the* cause of the necrosis and caseation of tissue: it is obviously **the influence of the bacillus**, which not only excites the cell-infiltration, and therefore induces such pressure on the vessels as the cells exercise, but which prevents the formation of new vessels, causes the obliteration of old—for these would remain in any "simple" though equally dense infiltration—and finally causes the death of the cells round about itself, for these might often be nourished from neighboring vessels.

In addition to the above, an important element in the causation of the retrograde changes of phthisis is probably that inherent weakness of the lungs (usually inherited) which not only renders them especial-

ly susceptible to injury, but also, when injured, renders them abnormally incapable of recovering from the inflammatory process which has been induced.

In many cases of phthisis also, especially in the more chronic forms, secondary inflammation and ulceration of the pulmonary consolidation, resulting from the injurious influence of retained secretions and inflammatory products, in which at this stage organisms other than the bacillus are often present, contribute to the destruction of the lung.

ETIOLOGY.—In studying the etiology of phthisis it is obvious, in the first place, that, accepting the tubercle bacillus as an essential element, something more is necessary for the production of the disease. The bacillus, as has been seen, must in some situations be constantly entering the lungs by means of the respired air (p. 315): in hospitals set apart for the treatment of consumption the sources of infection abound, and yet how exceedingly rare are the instances in which the development of phthisis in the healthy results! The other necessary factor is something inherited or acquired—**inherent in the individual.**

The influence of **hereditary predisposition** is so marked that it must necessarily occupy a prominent place in the pathology of phthisis. As to the nature of what is transmitted—although in quite exceptional cases this may possibly be the tubercle bacillus—speaking generally, it is in all probability simply a tendency to disease. It may be said that this tendency consists in some feebleness of the constitution in general, and often of the lungs and other organs in particular. As a result of this feebleness there is usually a want of constitutional vigor, the power of resisting injurious influences is diminished, and the lungs and often other organs and tissues which are especially weak are in consequence abnormally liable to become inflamed. Further, this inherited weakness not only renders certain organs abnormally liable to inflammation, but also abnormally incapable of recovering from the effects of the inflammatory process.

Another important factor in the development of phthisis is the state of the **general health.** Quite apart from any inherited feebleness, there can be no doubt that an impaired state of the general health greatly favors the development and progress of the disease. It is when *both* these obtain that we have the most favorable conditions.

In these two conditions, therefore, hereditary predisposition and state of general health, we have the other factor—the something inherent in the individual—which appears to be necessary for the production of phthisis. It is this **inherent** condition which must be regarded as constituting a soil favorable to the development of the inspired bacillus, and, whatever it may be, its importance is difficult to over-estimate.

So little is at present known of the life-history of Bacillus tuberculosis that the circumstances which favor its growth cannot be formulated; but in endeavoring to understand the favorable influence inherent in the individual in the case of phthisis we shall probably gain some help from the **apical distribution** of the pulmonary lesion.

The causes of this apical distribution are probably to be sought for in the diminished range of respiratory movement which obtains in the highest portions of the lungs. As a result of this diminished movement there is diminished aëration of blood, and in certain conditions of health a tendency to stagnation of the blood-stream in the pulmonary capillaries. The stagnation of the circulation may lead to more or less injury of the walls of the vessels, and a slight leakage be thus induced.

It is obvious that any inherited or acquired weakness must favor the occurrence of these apical changes. General feebleness and want of vigor lead to loss of muscular strength and weakness of the heart, and thus tend to prevent the full expansion of the chest, to cause a stooping posture of the body, and to impair the blood and air circulation—all conditions favoring blood-stagnation in the highest portions of the lungs. Further, the toneless condition of the blood-vessels and the poverty of the blood with which the constitutional feebleness is so often associated furnish the conditions which are the most favorable to transudation. May not the existence of such physical conditions in the highest portions of the lungs be essential to, or at all events greatly favor, the injurious influence of the inspired bacillus? And may we not, by treatment which tends to obviate them, do much to prevent the development of phthisis?

CHAPTER XLVI.

INFLAMMATION OF THE BRAIN AND SPINAL CORD, AND OF THEIR MEMBRANES.

INFLAMMATORY processes in the nervous centres are less frequent than was formerly supposed. Many of the morbid changes in the brain and spinal cord attended by softening, and formerly regarded as the result of inflammation, are now known to arise from simple interference with the blood-supply, such as results from thrombosis, embolism, or degenerative changes in the walls of the blood-vessel (p. 76).

Inflammation of the brain and spinal cord may begin upon the surface, being secondary to an inflammation of the meninges (**meningo-encephalitis**), or it may commence in the substance of the organs. Sometimes the process is diffuse, sometimes circumscribed. It may run either an acute or a chronic course, resulting in infiltration and softening, suppuration, (abscess), or sclerosis.

INFLAMMATION OF THE MENINGES.

ACUTE MENINGITIS or **MENINGO-ENCEPHALITIS.**—The latter name is the more accurate, for the cortex of the brain invariably participates in an inflammation of the meninges, and to this participation many of the symptoms of the disease are due. All the meninges are not equally involved. The disease has its seat in the vascular pia mater; the arachnoid also is affected, but the dura mater presents little or no change, unless the meningitis has arisen by extension from the middle ear, disease of the nose or of the skull-bones, in which case the dura may be inflamed or even gangrenous over the seat of the primary disease.

Etiology.—Whether primary or secondary to some other disease, we may feel certain that acute meningitis, in spite of a few obscure cases in which the etiology is quite unknown, is always due to the action of organisms. The two commonest forms are the **tubercular**, due to the development of "tubercles" along the Sylvian arteries (p. 320), and the **septic**, due to infection with septic organisms through

a wound or from some focus of septic inflammation, such as a suppurating middle ear or a syphilitic necrosis of the skull. Next it may occur as an epidemic disease—**epidemic cerebro-spinal meningitis**; and it may arise **in the course of certain infective diseases**—pyæmia, erysipelas, pneumonia, typhoid, etc. Rarely, meningitis (**simple traumatic**) arises after a blow not causing any wound, and it is said to have been found in some fatal cases of sunstroke: here we must assume the injury (from blow or heat) to have been the predisposing cause, enabling some organism accidentally present in the blood to settle and grow.

Morbid Anatomy.—The tubercular form affects chiefly the base of the brain (basi-meningitis), the tubercles being found on the inner surface of the stripped-off pia about the pons-peduncles, chiasma, and vallecula Sylvii; a few scattered ones may be found on the convexity. All other forms affect by preference the convexity of the hemispheres, but readily extend to, or even start from, the base. The spinal meninges are, as a rule, less affected than the cerebral; but it must not be supposed that the term "cerebro-spinal meningitis" implies that spinal meningitis occurs only in the epidemic disease.

The pia mater becomes extremely hyperæmic, as also (over a corresponding area) does the cerebral cortex, which softens from infiltration and usually presents small hemorrhagic foci. At the same time the subarachnoid fluid increases in amount, being usually rendered turbid by the escape into it of white and red corpuscles, and sometimes becoming actually purulent. In the hollows between the convolutions and in the interpeduncular space this turbidity is always most marked, and here masses of fibrin—sometimes firm, again soft and puriform—collect in the more intense cases of the disease, these being spots of least resistance like the grooves between the intestines in peritonitis. The arachnoid is turbid and slightly swollen.

The velum interpositum is hyperæmic and swollen, leading to effusion into the ventricles, which become distended with fluid; the convolutions are thus pressed against the skull and flattened. The ependyma thickens and becomes rough on the surface.

Pathology.—It will be seen that the stage of hyperæmia will account for the early delirium, excitement of the senses, and tendency to convulsive movements; that as the infiltration of the cortex goes on these subside and certain paralyses are apt to appear, either from injury to motor centres or to involvement of motor nerves after they have left the brain; finally, the increasing effusion into the skull and

rising intracranial pressure induces coma, as has been shown by a few cases in which fluid has been drawn off and the patients have recovered consciousness.

CHRONIC MENINGITIS.—The above are generally acute diseases, but *chronic* inflammations occur from alcoholism, in general paralysis, syphilis, and other diseases, leading to circumscribed thickenings of the membranes, adhesions of the membranes, and superficial sclerosis of the subjacent brain- or cord-substance.

Inflammation of the Brain and Cord.

ENCEPHALITIS AND MYELITIS.—Inflammations commencing in the substance of the brain or spinal cord are, as a rule, circumscribed; but in the cord it is not uncommon for myelitis to extend through a considerable length of the gray matter. According to Charcot, hemorrhage into the cord is generally the result of myelitis.

Etiology.—Mechanical injury causing contusions and lacerations is a common cause of round-celled infiltration and inflammatory softening; so also is pressure, as is best seen in the neighborhood of tumors, tubercular masses, parasites, etc. and in angular curvature of the spine. Cases occur also, especially in the cord, in which the cause of the inflammation is obscure. Suppuration in the cord is extremely rare, and due either to injury and septic meningitis, to bursting into the dura mater of a tubercular focus from spinal caries, or, most rarely, from septic embolism; in the brain it is more common, though still rare. In this situation the ordinary causes of abscess are three: (1) Direct injury to the head, sometimes of a slight kind and unaccompanied by wound, but generally fracturing the skull, producing a wound, and even leaving a foreign body in the brain-substance. (2) Disease of the skull-bones, especially of the petrous part around the middle ear. In these cases the membranes and brain may all be adherent to the diseased bone, and the abscess lie close to the surface, or the abscess may lie deeply in the substance of the brain and produce no disturbance of the membranes. (3) Pyæmia. The abscesses in these cases, which are rare, are often multiple. In a small number of cases cerebral abscess has been associated with dilated and ulcerated bronchi: if, as seems probable, there is a connection between the two diseases, the abscess must be embolic in origin.

Morbid Anatomy.—The process of inflammation in the brain is the same as elsewhere. It begins with hyperæmia, often accompanied by minute extravasations of red corpuscles; the tissue becomes infiltrated with fluid and leucocytes and considerably softened, so that it washes away under a stream of water too gentle to affect the healthy substance. At first uniformly red or mottled, the softened tissue gradually acquires a brownish or brownish-yellow color, owing to changes in the hæmoglobin. The nerve-fibres, nerve-cells, and cells of the neuroglia become fatty and disintegrate; the fat-granules are taken up by leucocytes, which grow into large very granular cells, called granule-cells or corpuscles of Gluge (Fig. 15). The above process is described as **inflammatory softening**, and is quite distinct from the degenerative softenings from embolism, thrombosis, etc. (p. 75).

If the cause is of such a nature as to lead to **suppuration**, cell-infiltration increases greatly, replacing the normal structure; then the centre of the mass dies, and a yellowish or reddish pus forms: in connection with the middle ear the pus is generally greenish and very offensive. Such an abscess may spread until it bursts either externally or into the ventricles, and if it be opened during this stage its walls will be found shaggy, very vascular, dotted with hemorrhages, and softer than normal; or it may at any time cease to spread and become surrounded by a capsule of connective tissue, whilst the pus often undergoes mucous degeneration and becomes thick and viscid. It is thought that pus thus encapsuled may dry up and caseate or calcify, or be even completely absorbed, leaving little more than a scar. Abscesses may occur in any part of the brain, but are most common in the temporo-sphenoidal lobes and cerebellum, because of the contact of these parts with the middle ear—the commonest source of infection.

Sclerosis of the Brain and Spinal Cord.

GENERAL ACCOUNT OF SCLEROSIS.—Many diseases are characterized by the presence of excess of fibrous tissue in different parts of the central nervous system, such excess being accompanied by degeneration and atrophy of the proper nervous elements. The abnormal tissue is just such as results from a productive inflammation (p. 259), and many pathologists regard these diseases as of inflammatory origin. There is, however, much room for doubt in

many cases, and other observers prefer to look upon the increase of connective tissue as due to a hyperplasia of the neuroglia, the cause being unknown. Most probably they are instances of overgrowth of connective tissue following upon degeneration and diminution of the physiological resistance of a higher tissue, being comparable to the growth of fat and connective tissue which follows on the disappearance of muscle-cells in pseudo-hypertrophic paralysis. As lesions of this nature produce *induration* of the parts affected, they are called **scleroses.** In their early stages, however, which are rarely seen, *softening* rather than induration results.

Sclerosis may be either **primary** or **secondary**—*i. e.* the fibroid overgrowth may first appear, and by its pressure cause atrophy of the nerve-tubules, or the primary lesion may be that rapid degeneration of nerve-fibres which follows their separation from the cells of which they are processes, the fibroid overgrowth being consequent upon this. These changes may affect either the brain or the cord, and may be more or less diffuse in distribution or limited to physiological tracts, such as the crossed and direct pyramidal; or small patches may be irregularly scattered through the part—disseminated or insular sclerosis. Either the gray or white matter may be the primary seat of the lesion, but in certain diseases the overgrowth generally extends from the one into the other, whilst in others such extension hardly ever occurs.

Naked-eye Appearances.—In the earliest stage a soft red patch, with more or less swelling, may indicate the seat of disease, but much more commonly the area is pale and grayish, its translucency and firmness varying with the relative proportions of cells and fibrous tissue present. The part may be swollen, of normal size, or contracted, and the pia mater is generally more or less adherent. Often, however, no naked-eye change can be detected in the fresh cord. This should always be cut into portions about half an inch long, kept together by the membranes on one side, and placed in bichromate of ammonia (2 per cent.). This stains the normal nerve-tissue greenish brown, whilst the sclerosed tracts remain pale yellow, and are easily detected and traced. In sections the altered tissue stains deeply with carmine. This is owing to the fact that the white substance of the nerve-fibres does not stain, but the connective tissue stains deeply. Hence the degree of staining is valuable as indicating, even to the naked eye, the degree of the sclerosis.

Microscopical Appearances.—In the cord it is almost always

possible to compare the diseased with healthy tracts. We then find, as a rule, that in the *white matter* the clear rings (substance of Schwann) which normally surround the axis-cylinders have disappeared in the former (Fig. 160), few if any axis-cylinders being visible in it, and the connective tissue has increased so as to more or less completely replace the lost medullary substance (Fig. 161). In rarer cases leucocytes are found infiltrating the patch, and exudation-corpuscles may be numerous. The walls of the blood-vessels (external coats) also are said to be thickened. In the *gray matter* intense hyperæmia is present in the early stages, and more or less round-celled infiltration. This is succeeded by fibroid overgrowth, such as the above. The nerve-cells may be swollen at first, but later on they are shrunken, often pigmented, and diminished in number, and not uncommonly the anterior cornu may be wholly destitute of them.

FIG. 160.

Section of Spinal Cord about the Eighth Dorsal Segment, from a Case of Locomotor Ataxy. There is sclerosis of the postero-external column and atrophy of the fine plexus of nerve-fibrils surrounding the cells of Clarke's column; moreover, a band of sclerosis is seen entering the column instead of the bundle of nerve-fibres. The cells themselves are atrophied and their processes destroyed. This case was of interest because, in connection with these lesions, the patient had well-marked visceral symptoms—gastric crises, bladder troubles, and laryngeal crisis—in addition to the ordinary ataxic symptoms. × 100 diameters. (Dr. F. W. Mott.)

SCLEROSIS OF THE BRAIN.—This is less common than sclerosis of the cord, both as a primary and as a secondary lesion. *Primary* scleroses of particular parts have not been associated with definite symptoms. The overgrowth may be general, but is usually disseminated. It is found in many cases of insanity, but most constantly in general paralysis of the insane, which is believed to be due to sclerosis of the gray matter of the cortex, which later extends into the white substance. It is frequent also in isolated convolutions, in the pons, and medulla of epileptics and idiots. As a *secondary* lesion a band of descending degeneration is found after destruction of the motor-fibres any-

where below the cortical centres, such destruction being most common in the basal ganglia, especially the corpus striatum.

FIG. 161.

Extreme Sclerosis of Spinal Cord. A transverse section, showing the atrophy and disappearance of the nerve-fibres, and the new tissue between them. × 200.

SCLEROSIS OF THE CORD.—In this part of the nervous system certain symptoms are associated with sclerosis of certain tracts. This may be primary or secondary, and may affect either white or gray matter.

White Matter.—Perhaps the best example of **primary** sclerosis of white matter occurs in locomotor ataxy. In this disease the naked-eye and microscopic appearances above given are found in the posterior root-zone (Fig. 160, and Fig. 162, *p. r. z.*), and are almost always most marked or present solely in the lumbar region. Commonly the sclerosis involves also the mesial portions of the posterior columns, and on the other hand the posterior nerve-roots and cells in the posterior cornu (lightning pains and anæsthesia). It may extend even to the lateral columns, causing motor paralysis. The process slowly extends up along the posterior root-zone; very rarely it may be most marked in the dorsal or cervical region.

FIG. 162.

Secondary Degeneration. Section through the cervical and lower dorsal regions of a cord destroyed by a fracture below the mid-dorsal region. The upper shows the ascending degenerations in the column of Goll and the cerebellar tract; the lower, the descending degenerations in the lateral and anterior columns. *c. g.* Column of Goll. *p. r. z.* Posterior root-zone. *c. t.* Cerebellar tract. *c. p. t.* Crossed pyramidal tract. *d. p. t.* Direct pyramidal tract. (Diagrammatic.)

Idiopathic lateral sclerosis is another example, the lateral columns being affected, as in the descending degenerations soon to be described. The sclerosis tends always to extend to the gray matter. Disseminated sclerosis also occurs in the cord, the symptoms varying greatly with the spots affected. An annular sclerosis sometimes results from meningitis in caries of the spine.

The secondary degenerations of the cord are frequent and important. They are divided into **descending** and **ascending**, the former affecting centrifugal tracts (motor), the latter centripetal (some kind of sensory). The motor tract runs from the cells of the motor cortical centres through the "internal capsule"

down the crus and through the pons into the medulla. Here most of it crosses in the decussation to the opposite lateral column of the cord (crossed pyramidal tract, Fig. 162, *c. p. t.*, and Figs. 163, 165), but a varying number of fibres run down along the anterior median fissure in the anterior column of the same side (direct pyramidal tract, Fig. 162, *d. p. t.*). These latter probably keep on passing to the opposite side through the anterior commissure, and the fasciculi have generally disappeared in the lower dorsal region. The crossed tract extends to the lower end of the lumbar enlargement. Removal of the motor cortical centres on one side will therefore cause degeneration of the whole motor tract springing from it, and lesions lower down will cause degeneration of the portion of the tract below them, more or less complete according to the number of fibres they damage. The tendency of the secondary lateral sclerosis to extend into the gray matter is much less than that of the primary, and atrophy of muscle is proportionately rarer.

Ascending lesions affect the columns of Goll (Fig. 162, *c. g.*, and

FIG. 163.

Section of Spinal Cord about Fourth Dorsal Segment. A tumor was pressing upon this part of the cord. There is sclerosis of the posterior median-postero extended partially, direct cerebellar, and crossed pyramidal tracts. The antero-lateral is partly sclerosed. Numerous black lines and spots indicate engorged vessels or hemorrhages. (Specimen and photo by Dr. F. W. Mott.)

Fig. 164), extending upward from the lower dorsal region, the direct cerebellar tract (Fig. 162, *c. t.*, and Fig. 163), running from the

second or third lumbar nerve to the cerebellum, and the antero-lateral tract (Gowers), of which many examples have now been shown, forming a thin ascending layer of degeneration on the lateral column in front of the direct cerebellar tract.

FIG. 164.

Sclerosis of the Posterior Median Columns only, due to spinal meningitis involving the posterior nerve-roots, fibres from which ascend, uninterrupted by cells in the posterior median columns. (Specimen and photo by Dr. F. W. Mott.)

The difference between the two sets of lesions is that the cells which govern the nutrition of the motor fibres are at their upper ends (cortical cells), whilst those which govern the nutrition of the sensory fibres are situate at their lower ends, in the gray matter of the cord (posterior spinal ganglion, posterior cornu, and Clarke's column?). The sketches (Fig. 162) were taken from a case of fractured spine a little below the mid-dorsal region, in which the patient lived seven months; they show the ascending and descending degenerations well. Statements vary as to the time at which the degeneration becomes apparent: Bastian says seven to fourteen days; Schiefferdecker found that in dogs it began after fourteen days, was well marked after four to five weeks, but no sclerosis was noted until the eighth week.[1] These statements are probably all too late.

Knowing the extent of these tracts, it is easy to see what secondary degenerations will result from a given lesion.

[1] Ross, vol. i. p. 844.

Gray Matter.—The great ganglion-cells of the anterior cornu are those which usually suffer primarily. They may be affected in large areas, and *acutely*, as in infantile paralysis and the acute spinal paralysis of adults, in which groups of muscles or all the muscles of one or more limbs become paralyzed; extension may occur for a short time, but as a rule it soon ceases. In the general spinal paralysis of Duchenne a similar lesion occurs less acutely, affecting as a rule the

Fig. 165.

Section of a Spinal Cord just below the Fourth Dorsal Segment, upon which a Gumma pressed. The crossed pyramidal tracts are markedly sclerosed; the direct pyramidal tracts were probably small in this instance, not reaching down to the level of section. In the postero-external columns a comma-shaped area of degeneration is seen. (Dr. F. W. Mott.)

cells connected with the lower limbs first, and spreading in the course of weeks or years to all the voluntary muscles, affecting them in groups and causing rapid wasting of them. The process may also be *chronic*, spreading slowly, not affecting large groups of cells, but a few at a time, so that individual muscles waste progressively, fibre by fibre, and paralysis comes on slowly, as in progressive muscular atrophy. It is, however, right to say that these lesions have not been found in all cases of this disease, and it is believed by many that the disease may have also a peripheral origin, being probably allied to cases of Duchenne's pseudo-hypertrophic paralysis, in which central lesions have but rarely been found.

In describing sclerosis of the white columns we have already mentioned that the disease often secondarily involves the gray matter—*e. g.* in tabes dorsalis and lateral sclerosis. Again, it is a common mode of ending in these diseases for the sclerosis to extend to the medulla and destroy the cells of the all-important nuclei situate there. These nuclei suffer also primarily in glosso-labio-laryngeal paralysis.

RESULTS OF SCLEROSIS OF WHITE COLUMNS.—In conclusion, it is necessary to remind the student that it is hopeless to attempt the diagnosis of the seat of nervous lesions without an accurate knowledge of anatomy and of nerve physiology. With regard to the cord the following facts will be found useful:

The **antero-lateral columns** convey motor impulses from the cerebral cortex to the cells of the anterior cornu by means of the direct and crossed pyramidal tracts. Other fibres (anterior root-zone) are believed to have a looped arrangement, connecting cells of the anterior cornu at different levels, and probably aiding in co-ordination. Lesions of the descending tracts in these columns offer impediments to the passage of cerebral impulses, and cause tremors, paresis, paralysis, or, if irritant, rigidity or spasm. The functions of the cerebellar and antero-lateral tracts are unknown, but they are ascending tracts in relation with posterior nerve-roots, and are almost certainly sensory paths; and the cerebellar tract probably conveys impulses from the viscera, as its fibres are divided from that bundle of each posterior root which runs to Clarke's column, and then through the posterior cornu and crossed pyramidal tract to the cerebellar tract on the surface of the latter.

The **posterior columns** consist of the fasciculi of Goll or posterior median columns of which the function is unknown, and of the posterior root-zone. The latter contains, in the lumbar region at least, afferent fibres of ordinary tactile sensation, and others which convey impressions of temperature and pressure and of muscular sense; also sensory fibres from the sexual organs. Interference with these columns will produce inco-ordination (from loss of muscular sense), diminution of sexual desire, and other obvious results (Fig. 160).

With regard to the **gray matter**, the cells of the **anterior cornu** are motor. Destruction of them causes paralysis of the muscles they supply, followed by rapid atrophy of the nerves and of the muscles. The cells of the **posterior cornu** are concerned in sensation, and especially in the transmission of **painful** impressions. The gray

matter of the cord contains also many centres—*e. g.* the oculo-pupillary in the cervical and upper dorsal regions, vaso-motor centres throughout the cord, centres governing the peristalsis of the alimentary tube, others preserving the tone of the sphincters vesicæ and ani, others in the lumbar region superintending micturition, defecation, erection, ejaculation of semen, and parturition. All that is known of these centres is that they are not in the anterior cornu (Ross), for lesions of these cells do not affect them. Ross believes that the visceral centres are in Clarke's column, the cells here being large and bipolar, like those of the sympathetic, and the tract existing as a column only in the dorsal and upper lumbar regions, where visceral nerves are given off. In series with these scattered cells are found both in the sacral and cervical regions. The head of the column is the nucleus of the vagus, the chief of visceral nerves. These centres may all be affected by lesions.

The **posterior root** conveys sensory impressions: lesions of it will produce anæsthesia, dysæsthesia, hyperæsthesia, pain, etc. The **anterior root** conveys motor impressions: lesions of it will cause tonic or clonic spasms, paresis or paralysis, with rapid atrophy of nerve and muscle beyond.

Reflexes are of two kinds—**superficial** or **cutaneous, deep** or **tendon reflexes.** The latter are probably stretch-contractions, not true reflexes, but they occur only under conditions favorable to reflex action. In every reflex an afferent and an efferent nerve, together with a centre (*reflex arc*), are concerned. In disease reflex excitability may be increased or diminished. It will be increased by anything which lessens the resistance to the passage of the stimulus. Excitation of the cornual cells by strychnia has this effect; so, too, has removal of cerebral influence, as by sleep or disease of the lateral columns. It will be diminished by obstruction to the stimulus, as by sclerosis of the posterior root-zone invading the nerve-roots or destroying the posterior cornual cells, or by damage to the anterior cells or nerve-roots; by some sedative drugs, as bromide of potash; or by increased cerebral control, as by an effort of the will.

CHAPTER XLVII.

SEPTICÆMIA AND PYÆMIA.

THE diseases known as **Septicæmia** and **Pyæmia** result from the absorption and dissemination of substances derived usually from the septic discharge of some wound or acute inflammation. The two diseases are frequently associated.

By "septicæmia" is now generally understood those forms of septic disease which are unaccompanied by the development of secondary inflammations. "Pyæmia," on the other hand, no longer means disease due to the absorption of pus into the blood, but includes cases of septic disease characterized by the presence of secondary or metastatic suppurations. These two maladies are the chief elements in the excessive mortality in large surgical hospitals, and nothing is more clearly established than that overcrowding of patients with septic wounds is, indirectly, their chief cause. By this process the diseases may speedily be generated anywhere. In almost all cases of both diseases there exists a wound to which unpurified air or some germ-bearing finger, instrument, or dressing has gained access, or which may have been inoculated directly from a similar case.

The pathology of these diseases has been worked at by many observers, but the results obtained were too uncertain and too often contradictory to be of much value until the appearance of R. Koch's small book on *Traumatic Infective Diseases*[1] in 1878. In this work Koch made known methods of research which were vastly more certain than any which preceded them, and which have since been improved upon. His account of the results which were attained by these methods, and the admirable Report on the Nature and Causes of Pyæmia, Septicæmia, and Purulent Infection presented to the Pathological Society in 1879 by a special committee,[2] will be freely utilized in the present chapter.

SEPTICÆMIA.

EXPERIMENTAL RESEARCHES.—Koch injected five minims of blood or meat-infusion, in an early stage of putrefaction, under the

[1] Translated by Cheyne, New Sydenham Society.
[2] *Trans. Path. Soc. Lond.*, 1879.

skin of a house-mouse: the animal at once became restless and ceased eating; its movements soon became weak and uncertain, respiration irregular and slow, and death occurred in four to eight hours, or even earlier, the time of its occurrence varying with the size of the dose. No pathological change was found in the body, and blood inoculated on healthy animals produced no effect. The disease was not infective. We have here a disease due to the absorption into the blood of putrid material, not characterized by secondary inflammation; it is therefore a septicæmia. It seems to be due to the presence of a chemical poison in greater or less quantity in the blood, and is comparable to the result of the injection of a poisonous alkaloid. This would exercise its specific action upon the organism, and would, of course, not multiply in the body: the original dose being diluted by the blood-mass, a few drops of the latter injected into a healthy animal would have no effect. This form of septicæmia is called **Septic Intoxication** or **Sapræmia.** From an extensive series of experiments Sanderson gives the following as its symptoms: Restlessness, muscular twitching, and increasing weakness till the animal falls; vomiting and profuse diarrhœa, the feces being at first loose and whitish gray, but later bloody; the temperature rises some degrees at first, often falling below normal before death; respiration and heart-action gradually fail; and death is sometimes preceded by cramps. The corresponding post-mortem appearances are: blood dark, feebly clotted; petechiæ beneath peri- and endocardium and pleura; intense staining of the endocardium and lining membranes of the great vessels, and often a little blood-tinged serum in the serous cavities, both soon after death, indicating destruction of red corpuscles even during life; intense congestion and ecchymosis, with shedding of the epithelium of the mucous membrane of the stomach and intestines; spleen swollen, soft, and pulpy; liver often swollen and congested.

As would be expected, when less poison is introduced the resulting symptoms are less marked, and are quite absent when one, or at most two, drops of putrid blood have been injected. After the use of such small quantities of blood mice often remained permanently well. But about a third of them sickened after about twenty-four hours, the symptoms being characteristic and constant, and not preceded by the above toxic effects. They were as follows: Dulness of the eye, with increased conjunctival secretion, finally gluing the lids together; the animal moved little and languidly, and generally sat still in a peculiar attitude; it ceased to eat, its respirations became slower, weakness

steadily increased, and death came on almost imperceptibly forty to sixty hours after inoculation. Post-mortem, there were found slight œdema, which is often absent, at the site of injection or inoculation, and considerable swelling of the spleen, other organs appearing normal.

It is sufficient, in order to cause death in about fifty hours and with similar symptoms, to touch with a knife at the point most remote from the seat of inoculation the subcutaneous tissue of a mouse dead of the disease, and with this knife to scratch the ear of a healthy animal.

Here, again, we have a disease which must, according to our definition, be called septicæmia. But it differs from that form first described in being intensely *infective.* Only a minute quantity of poison is introduced—quite insufficient to produce toxic effects—and it multiplies enormously in the blood. Some twenty-four hours of incubation pass whilst its development reaches a certain stage; with its further increase the symptoms become more severe. This form is known as **Septic Infection.**

The blood of animals which died after *injection* of 1–10 ♏ of putrid blood generally contained varying numbers of cocci, bacteria, and bacilli, but after *inoculation* it contained only small bacilli. These were present in large numbers, most white corpuscles containing one or many of them. Koch thinks they grow into the vessels about the seat of inoculation, and become generalized in this way; he has never seen them in lymphatics. They occur in all parts, and are not more numerous in the swollen spleen than elsewhere.

Koch failed to infect either rabbits or field-mice with this disease. The latter result seems very curious; but Koch points out that there are obvious differences between the blood of the two animals, so it is easy to imagine that differences may exist which render the blood of the one suitable, that of the other unsuitable, for the development of these particular fungi.

Under the heading "Septicæmia" we have therefore two diseases—**septic intoxication** or **sapræmia,** non-infective, due to the absorption of a chemical poison manufactured in some putrefactive process external to the body; and **septic infection,** due to the entry of specific fungi into the blood and to their multiplication there. The organisms act by producing poisonous substances in their growth, but these products are not irritant, and therefore no secondary inflammations arise. The fungi which characterize the septicæmia of one animal differ from those which occur in that of another—*e. g.* bacilli in

mice, oval cocci in rabbits. Every putrid fluid probably does not contain the organisms of each of these diseases. The production of septic infection from putrid fluids is therefore uncertain. Thus Koch notes that on two separate occasions he succeeded with putrid meat-infusion in producing in rabbits the same disease, characterized by the same cocci.

OBSERVATIONS ON MAN.—In man the occurrence of analogous forms is *a priori* likely, and cases might be quoted in which the existence of pure septic intoxication or septic infection was very probable; but the subject has not been at all fully worked out. Clinically, it is usually impossible to diagnose between them, and the post-mortem signs are very similar. The symptoms of septicæmia in man are fever, often beginning with a rigor, which may be repeated, especially in the infective form—all the symptoms of fever, including delirium, sometimes violent, passing on to stupor or even coma. There are great loss of strength, rapid emaciation, dry tongue, and rapid, feeble pulse; the "typhoid" state appears early. Vomiting is common, diarrhœa much less so, but cases do occur in which the symptoms and pathological changes of gastro-enteritis are well marked. A jaundiced tint of skin is not uncommon, and petechial spots may occur. Albuminuria is frequent. In the infective form death occurs quietly in a semi-comatose state and after a longer period than the non-infective, the characteristic ending of which is speedy collapse—the patient dying with some dyspnœa and all the symptoms of rapid cardiac failure.

The red corpuscles in blood drawn during life run into clumps instead of rouleaux; and Hüter states, as the result of observations on the palpebra tertia of infected animals and on the lip of man, that in septicæmia there is widespread capillary stasis, perhaps half the capillaries in a district being full of resting blood in severe cases. Frequently, too, small clumps of red corpuscles pass across the field or stick in some vessel.

The **post-mortem signs** are: Feeble rigor mortis and early decomposition; the blood may be dark and fluid, but is more often clotted, as usual; soon after death there is deep staining of the endocardium and lining membrane of the great vessels, and any serous fluid in the pleuræ or pericardium will be blood-tinged: this is owing to rapid disintegration of red corpuscles, which begins even during life; petechiæ occur beneath serous membranes, chiefly on the back of the heart and under the pleura; hypostatic congestion of the lungs and

congestion of the abdominal viscera would be expected under the circumstances; the spleen is markedly swollen and often pulpy; and, lastly, the mucous membrane of the alimentary canal may be congested or much more rarely inflamed.

Organisms, especially cocci, have often been found in various parts and organs in septicæmia; they have also often been missed. Even when found no characteristic form has been shown to be present.

Marcus Beck calculates, from the result of experiments on dogs, that one to two ounces of putrid serum or pus would be required to kill an adult man by **septic intoxication.** This form can, therefore, occur only where *large cavities* exist and *are imperfectly drained*—*e. g.* in bad compound fractures, wounds of joints or pleuræ, abdominal sections, the uterus post-partum, etc. Such cavities cannot always be drained; hence the necessity for also preventing putrefaction. Raw surfaces and serous membranes are well known to be excellent absorbent surfaces. A large quantity of poison may be taken up by them in a short time. Granulating surfaces, on the other hand, have been shown by Billroth not to absorb the putrid poison. Hence **septic intoxication** will be most likely to occur *before granulation begins.* It may occur later if the granulation-tissue is destroyed in any way. No line can be drawn between it and septic traumatic fever (p. 299).

Septic Infection may occur from the smallest wound, and there may be distinct evidence of inoculation of a poison. The presence of only a *small wound* is evidence of inoculation of an infective poison.

With regard to the cause of septic intoxication, many of the products of putrefaction are pyrogenous. Bergmann succeeded in crystallizing in fine needles from putrid fluids an alkaloidal body which he calls sepsin, which possesses in a high degree the property of exciting fever.

PYÆMIA.

Pyæmia differs from septicæmia in this respect, that in it the absorption and dissemination of the poison give rise not only to a general disease, but also cause the formation of secondary foci of inflammation—so-called **metastatic abscesses.** These are the distinctive pathological characteristics of the disease. Its clinical symptoms are well marked, the very irregular temperature being most important; but it is confessedly complicated with more or less septic poisoning.

Like septic infection, the disease is essentially a hospital disease, and the poisons are probably similar; some, indeed, believe them to be the same. The source of infection is almost always some wound or inflammation, generally suppurating, the discharges not being aseptic. But there may be no wound, as is seen in acute infective periostitis, infective endocarditis, and rare cases of "spontaneous" pyæmia, in which no primary lesion can be found. In these cases the poison has probably entered through some healthy mucous membrane. As in septicæmia, it gains access to, and is distributed by, the blood.

Besides the secondary abscesses, the following signs may be found post-mortem: As in all septic disease, rigor mortis is feeble and decomposition early. Emaciation is generally marked, and the skin yellow or jaundiced. Petechiæ may be present. The wound, if there is one, is sloughy, perhaps surrounded by diffuse inflammation, and offensive; any bone which has been divided shows the appearances of septic osteomyelitis. The thrombi in the veins leading from the focus of infection are extensive, and undergoing infective puriform softening; the end of one or more thrombi perhaps projects into a large vein in which circulation was going on. The blood is generally normal to the naked eye, but microscopically contains excess of leucocytes. Hypostatic congestion of the lungs is generally present, the spleen large and pulpy, and the liver and kidneys show "granular degeneration."

The secondary abscesses are of two kinds—those which follow upon infarction, and those in which there is no evidence of such an antecedent change. In either case the occurrence of suppuration implies the presence of a strong irritant acting for some time, and it has been already pointed out (p. 282) that most irritants of this kind are fungi. It is probable that several fungi are capable of exciting suppuration, and they would therefore, if generalized by the blood-stream, produce the abscesses of pyæmia. It seems possible, therefore, that, for example, the organism which produces acute necrosis may not be the same as that of ordinary pyæmia from wounds. The *Streptococcus pyogenes* (p. 282) is the organism most often present.

However this may be, in the first kind of abscess infarction is induced by the lodgment in a terminal artery of a portion of infective clot. The mode of formation and characters of the infarct and abscess have been described on pp. 230 and 263. The preparation

for embolism has been noted above in the account of the veins leading from the focus of infection. These embolic abscesses are by far most frequent in the lungs, next in the liver, spleen, kidneys, and brain. They may occur in any vascular part. They lie generally upon the surface of organs, with their bases immediately beneath the capsule. They vary in size between that of a chestnut and that of a split pea, are usually multiple, and may be very numerous. They are surrounded by the usual hyperæmic ring. Often more than one organ is affected, and these abscesses may occur with others of the next kind. Sometimes the lungs are not affected when other organs lying beyond them on the blood-path are.

The second kind of abscess is a diffuse suppuration in the subcutaneous and intermuscular connective tissue in the joints and serous membranes. They are all tolerably common, and may occur alone or combined with the first variety. In these cases the irritant must be conveyed to the spot by the blood and settle there, probably because the nidus is suitable, or perhaps some capillary embolisms are the cause.

Pyæmia has never been produced in animals by the injection of blood or pus of pyæmic patients. Cocci and zooglœa masses are found in abundance on the surfaces of the focus of infection, the intensity of the process varying with their number, according to Birch-Hirschfeld. They have been traced into the surrounding tissues and have been seen piercing the wall of a vein. They have been found in the nearest lymph-glands, in all metastatic abscesses, and in many organs. They lie in capillaries or small arteries primarily, but soon pass out into the surrounding tissues.

Koch injected ten minims of putrid fluid, in which a portion of skin had been macerated, into a rabbit. No symptoms followed for two days; then the animal ate less, became weaker, and died one hundred and five hours after the injection. A purulent infiltration occupying the abdominal wall far around the point of injection was found; the inflammation had extended to the peritoneum, and there was general fibrinous peritonitis. The spleen was much enlarged, the liver had a grayish mottled appearance, and showed on section gray, wedge-shaped patches. In the lungs were some dark-red patches about as large as a pea, and airless. Animals inoculated with the blood of this one died of precisely the same disease. The smaller the dose the longer the time before death. This is explicable only on the supposition that the infective particles in the blood must reach

a certain number in proportion to the body-weight before they can cause death. Micrococci were found everywhere, especially in obviously altered parts. They adhered to the interior of vessels, often plugging them. Red corpuscles adhered to the coccus colonies, which seem able to induce coagulation; small thrombi are thus formed, which may be swept away as emboli, and would prove infective. Perhaps something of this kind may account for the second kind of abscess, but against this is the fact that pyogenic cocci are sometimes found in human blood, causing no such aggregations and no suppurations (p. 276). The resemblance of the whole disease to pyæmia is very marked. It is not certain, however, that pyæmia in man is *always* infective; *i. e.* the secondary abscesses *may* be due to emboli of putrid clot containing only non-pathogenic organisms, incapable of growing among active tissues or in the blood.

CHAPTER XLVIII.

THE VEGETABLE PARASITES.

PARALLEL BETWEEN FERMENTATION AND INFECTIVE DISEASE.—It has long been thought that the group of acute specific diseases must have a very special cause. The characteristics of this group are: That they occur epidemically; that they are obviously contagious and infectious; that each member is absolutely distinct from its fellows and runs a very typical course; and that the poison which gives rise to each of them multiplies in a marvellous manner: a single case of one of these introduced into a community may cause the death even of millions. Nothing could be discovered by the senses to account for the appearance of these diseases, yet they were obviously produced by something which multiplied in the sick, which clung about his clothing, etc., perhaps for long periods, and which could be carried through the air for considerable distances. This "something" is called the "**contagion**" of the disease, and for many years science has been endeavoring to discover its nature. It early became obvious that no gas would meet the requirements of the case, for diffusion would soon put an end to its power for mischief; a fluid was not to be thought of; so contagion was necessarily regarded as a solid in a state of very fine divis-

ion—*particulate*. It has been shown to be insoluble in fluids in which it can live by subsidence (vaccine, Chauveau), and by filtration, the poison not passing through the filter. These facts, taken with its power of multiplication, seemed to show that the contagium was some living organism; hence the origin of the **contagium vivum** or **germ** theory of disease, promulgated in a very crude form even in the Roman era. In 1840, Henle[1] clearly formulated the doctrine that living organisms, probably of a vegetable nature, were the causes of the acute specifics, and supported the view by arguments which have withstood all endeavors (and they have been many) to refute them. In 1838, two years earlier, Bassi and Audouin had discovered the fungous nature of the muscardine disease in silkworms; and in 1836, Schwann and Cagniard de Latour had independently discovered that yeast, the apparent cause of alcoholic fermentation, consisted of cells multiplying by budding and apparently of vegetable nature. They surmised that the decomposition of the sugar into alcohol, carbonic acid, etc. was connected with the growth of this plant, and in this view Henle heartily concurred.

Long before this it had been noticed that a close parallel might be drawn between an infective disease and a fermentation. It may be presented thus:

Infection	Addition of ferment.
Incubation	Period during which nothing is noticed.
Fever, outbreak, and course of disease	Rise of temperature and active fermentation.
Decline of disease	Gradual cessation.
Period of protection from same disease	Addition of more ferment has no effect.

It may be further noted that, except in cases in which yeast was added to the saccharine liquid, the source of the ferment in cases of alcoholic fermentation was as mysterious as was the source of the poison which gave rise to an epidemic of whooping cough.

ETIOLOGY OF FERMENTATION.—The above parallel was generally recognized, and the cause of fermentation, being much more open to experiment than the cause of infectious disease, was taken up by many workers. Many kinds of fermentation were speedily recognized—lactic, butyric, viscous, etc.; and the close relation of putrefaction to these processes was soon acknowledged. In each one of these organisms were found, and their relation to the processes has been

[1] *Pathologische Untersuchungen.*

the moot-point between the upholders of the *vital* or *germ theory* of fermentation and the supporters of the *physical theory*. The alcoholic fermentation has been used as the type of all.

The Germ Theory, started by Astier, Spallanzani, Schwann, and Cagniard de Latour, and perfected by Pasteur, is adopted by the great majority of scientific men at the present day. According to this view, the Saccharomyces cerevisiæ (yeast-plant) is the *cause* of the alcoholic fermentation. Its food is sugar, together with nitrogen and some inorganic materials, which must also be provided; the products of its life-action are alcohol, carbonic acid, glycerin, and succinic acid. It is supposed that the food-stuffs pass into the cells, which take what they require for their own growth and repair, and throw back into the fluid the products of their action. Thus, a yeast-cell forms the above-mentioned substances, just as a hepatic cell forms the constituents of bile. There is no reason whatever for classing the fermentations as distinct from the chemical changes effected by cells in general. The division was made before their nature was understood, when the insignificance of the cause and the greatness of the result were the striking features, and when the causal relationship between the growth of living organisms (or the presence of a substance derived from them—*unformed* ferment) and the chemical changes had not been proved.

The Physical Theory, started by Willis in 1659, and perfected by Liebig, affirms that fermentation is a "molecular motion" transmitted to unstable organic compounds (fermentable substance) by albuminoid particles (ferment) which are themselves the seat of "motor decay" (*i. e.* are undergoing decomposition). The molecular motion of these particles may initiate in a large amount of a more stable substance changes similar to those of which they are themselves the seat. Any portion of the substance to which this molecular motion has been communicated is capable of transmitting it to other suitable material, and thus the ferment *seems* to multiply. The ferment communicates its vibrations to the particles with which it comes into contact, and these again to particles next beyond, more slowly but in the same way as a spark causes the decomposition of a train of gunpowder. Bastian says that there is no proof of multiplication other than occurs in a sufficiently strong solution of sulphate of sodium when a crystal of the same salt is thrown in. Gerhardt thus illustrates Liebig's views: Every substance which decomposes or enters into combination is in a state of movement (molecular). Various forms of mechanical agitation provoke this movement (*e. g.* decomposition of chlorous acid, chloride

of nitrogen, fulminating silver); therefore chemical decomposition, in which the agitation is more complete, should produce such effects more strongly. It is known that platinum remains stable in nitric acid, but if silver also (which dissolves in nitric acid) is present, the platinum is dissolved; again, pure copper is not dissolved by sulphuric acid unless zinc is present. A solution of dextrin is not acted on by yeast alone, but when sugar is added to the fluid a great part of the dextrin shares the fate of the sugar, the motion of the atoms of sugar having been transmitted to those of the dextrin. By analogy, Liebig supposes that sugar does not change when quite alone, but decomposes—*i. e.* ferments—when in contact with a nitrogenous body (ferment) undergoing change. This view originated long before the *constant* presence of specific forms of organisms in every fermenting substance was demonstrated. Before Liebig died, however, Pasteur had gone a great way toward this; and in his last paper[1] on the subject Liebig, though still fighting against the germ theory, states that it is not opposed to the molecular-motion theory which he advocated; the decomposition would still be due to molecular motion transmitted to the fermenting substance by living protoplasm instead of decaying albuminoid material.[2] As nothing is known of the force by which living cells effect chemical changes, it is impossible to confirm or to refute this statement, but views as to the nature of vital action are beside the question we are considering.

It is very difficult absolutely to disprove the physical theory. Its supporters admit the frequent presence of organisms in fermenting fluids, but regard them as accidents or as spontaneously generated (Bastian), for the same decompositions can in some instances be effected in their absence. Thus dilute alcohol run over wood-shavings or charcoal so as to expose a large surface to air is converted into vinegar. But this is no evidence against the ability of the Mycoderma aceti also to effect the oxidation as a vital act; and indeed distinct differences exist between the two processes.[3]

On the physical theory much was made of the fact that spontaneous fermentations are always more or less impure, many germs of different form or habit being found in the fluid besides that which is essential to the particular fermentation; and, again, organisms indistinguishable by the microscope were found in fluids undergoing very different decompositions. From such facts it was argued that there was no

[1] *Ann. d. Chemie u. Pharm.*, vol. cliii. p. 1, 1870.

[2] Quoted from *Beginnings of Life*, Bastian.

[3] Schützenberger, p. 237.

constant relation between any one germ and a particular form of decomposition. The predominance of one characteristic form was accounted for by supposing that the conditions in each favored the growth of a certain organism or the origin *de novo* of a certain fungus (Bastian). But it has now been shown in very numerous instances that it is possible to obtain a cultivation of *each* of the various organisms found in a fermenting fluid, and to demonstrate that a special decomposition occurs only when one particular form of germ is present, all other forms being more or less variable and accidental impurities. And it has been shown also that organisms indistinguishable from each other under the microscope may give rise to very different chemical products when grown upon the same culture-medium, and may produce absolutely different results when inoculated upon animals of the same species. It is clear, therefore, that similarity of external form does not imply identity.

A pure cultivation of an organism is obtained by inoculation of a culture-ground with a pure needle dipped into the fluid containing the organism. The organism grows, and from the *margin* of the patch formed by it a fresh culture-ground is inoculated with a needle-point. This may be repeated any number of times. Germ-theorists believe that by this process they have eliminated everything taken from the original fermentation except the organism which is capable of growth; and they have endeavored to make this still more certain by washing the organism with sterilized water and other fluids incapable of destroying it, by filtration, by drying: after all this they show that inoculation of a suitable fluid with the purified organism invariably leads to the characteristic fermentation. But it is obviously *possible* that "particles in a state of motor decay" were in the first and each succeeding instance inoculated upon the culture-ground with the organisms, and that they too practically multiplied by communicating their molecular motion to the molecules of the culture-ground.[1]

Nevertheless, germ-theorists have rendered it certain that these "particles in a state of motor decay" adhere *very* closely to the organism which is constantly present, and are able to impart their

[1] Innate power of increasing or growing is not conclusive of life. Liebig pointed out that a small quantity of oxalic acid will act upon a very large quantity of oxamide, splitting the latter into oxalic acid and ammonia: one might say that, supplied with suitable pabulum, the oxalic acid increases indefinitely. Baumgarten says the difference between the chemical changes effected by oxalic acid and by living organisms is that the former acts by *juxtaposition* and the latter by *intussusception*; but this may mean only juxtaposition with internal tissues.

molecular motion to such substances only as this organism will grow in. For if the organism dies no fermentation occurs.

Moreover, the particles in a state of motor decay have never been demonstrated apart from organisms. So-called "antiseptics," which are selected on account of their ability to destroy the lower organisms, invariably check the molecular motions of the physical ferments: so also does heat sufficient to destroy organisms. In fact, the properties of the physical ferments are those of organisms.

Finally, it has been shown of several fermentations that the thinnest membrane, the shortest column of fluid, is sufficient to prevent the transmission of these supposed vibrations; that direct contact with the ferment is necessary; and that sonorous vibrations have no influence upon fermentable substances (Dumas). If a solution of sugar in a test-tube is divided into two parts by a plug of cotton-wool, and yeast is introduced into the upper, this only ferments, though *fluid continuity is uninterrupted.*[1]

Although the physical theory may be theoretically possible, the progress of discovery has shown that its rival, the vital theory, is the true one. To believe in the physical theory one must set aside a perfectly satisfactory and evident cause (the organisms) and proceed to support one hypothesis by another. We therefore conclude that *all the processes generally known as fermentations and putrefaction are due to the action of vegetable organisms.*

How do these Organisms Act?—The four following views are held:

(1) Like all living cells they require certain materials for the repair of their substance and for growth. They take into their substance the organic and inorganic compounds which are necessarily present in any liquid in which they will grow, and they throw back into the fluid the products of their action upon these compounds.

(2) Pasteur has stated that fermentation in general is a consequence of the life of ferments without free oxygen. They require oxygen so much that they take it from the organic substances, and thus split them up.

(3) Certain, but not all of them, produce *unformed* ferments—so called in opposition to the cells themselves, which are the "formed" or "organized" ferments. The chief characteristics of these bodies are—that they seem to act by mere contact ("catalytically"), not taking any part in the decompositions to which they give rise; that

[1] Hoffman, *Ann. d. Chem. u. Pharm.*, vol. cxv. p. 228.

they act in extremely small quantity; do not multiply, but nevertheless transform many times their weight of the fermentable substance, though ultimately they become exhausted; that they are soluble, and are always derived from living cells; that they all require water or moisture to act, some preferring an acid, others an alkaline reaction; that, like cells, they act best at a certain temperature, their action being arrested at a low or high temperature. They are complex albuminoid bodies, but have not been isolated in sufficient quantity for accurate analysis. Ptyalin, pepsin, trypsin are well-known examples from the human body; emulsin (bitter almond) and diastase (barley), from the vegetable kingdom. It is certain that some bacteria (*e. g.* putrefactive and pyogenic cocci) form amylolytic and peptic ferments, which can be separated from, and will act in the absence of, the organisms. Musculus has separated from Micrococcus ureæ a body capable of changing urea into ammonic carbonate. Yeast by an unformed ferment transforms cane-sugar into glucose and lævulose before converting it into alcohol, etc., but this latter change is not known to occur in the absence of living cells. Whether acting upon hydrocarbons or albuminoids, it is believed that these ferments generally cause simple taking up of water and splitting of the compound. It has been suggested that their action is that of a carrier, like hæmoglobin, or like the sulphuric acid in the manufacture of ether from alcohol.

(4) Nägeli has adopted the view to which Liebig seemed tending—that the life and growth of cells are necessary to fermentation, the chemical changes being always due to the transmission of the molecular motions of *living* protoplasm to the unstable compounds around it.

Products of Fermentation.—It is impossible to say much in a general way of the products of fermentative processes, for they are as various as are the processes themselves and the organisms which are believed to give rise to them. They are formed by processes of oxidation and deoxidation, of hydration, and of simple splitting up. The same food will, under the action of different organisms, be converted into very different substances. Thus, sugar undergoes vinous, lactic, and butyric mucous and mannitic fermentations. Other products than those from which the process takes its name are always formed. Gases are sometimes evolved, sometimes not. In all processes bodies are formed which hinder the development of, and ultimately destroy, the organisms which produce them; thus, the alcoholic fermentation

is checked by accumulation of alcohol, and putrefaction by the development of bodies like carbolic acid and cressol. It will be remembered that animals, too, produce bodies which tend to destroy them—*e. g.* carbonic acid.

If the analogy pointed out on p. 471 between infective diseases and fermentation were certainly true, we might at once infer that the former are caused by the growth and life-action of vegetable organisms in the tissues of the body, especially as many low forms of vegetable life have been found in connection with diseases in man and animals. But no one could accept the conclusion on the evidence of so superficial a resemblance. The same stringent proofs must be afforded in the case of each disease as were demanded in the case of each fermentation. How far these proofs are forthcoming will be shown in the concluding part of the present chapter. We shall now state shortly what is known of the botanical position and life-history of the vegetable parasites of man.

Natural History of the Vegetable Parasites.

The vegetable organisms which have been found connected with the diseases of man are all **Thallophytes**, or plants in which no distinction between stem and leaf exists; and, as they are all destitute of chlorophyll, they belong to the class of **Fungi,** *not* Algæ. The pathological fungi are of three kinds—**Bacteria** or **Schizomycetes, Yeasts** or **Blastomycetes,** and **Moulds** or **Hyphomycetes.** The bacteria, besides causing putrefaction and several of the "fermentations," include almost all the organisms which are believed to produce the infective diseases. They are therefore by far the most important group.

The **Schizomycetes** or **Fission fungi** are, with very few exceptions, achlorophyllous, non-nucleated, unicellular (with some exceptions) organisms, many of which approach the limits of microscopic visibility, whilst all are very small. They refract light strongly, and cause turbidity of any culture-fluid in which they may be. They are usually colorless, white or grayish, in masses. A few are green from chlorophyll: many are brightly colored, red, blue, yellow, etc., the envelope being certainly tinted, but the protoplasm being in too small mass to show any tint. Some forms are stained brown by iron

salts in water. The starch reaction with iodine is not rare. They consist of a peculiar form of protoplasm, *mycoprotein* (v. Nencki), and appear structureless; but it is very probable, from their great resistance to alkalies and dilute acids, that they possess a cell-membrane of a carbohydrate allied to cellulose. After the action of tincture of iodine, which stains and causes shrinking of the protoplasm, and during the formation of spores, a fine membrane may be actually seen. It is very elastic, and seems to be a firm inner layer of a gelatinous envelope, by more or less of which all bacteria are surrounded (see below). In form they vary much, being round, oval, dumbbell-shaped, rod-shaped, straight, wavy, or corkscrew-like; and, having these forms, the organisms may be, relatively, small or large.

Single round cells have no movement other than Brownian, but chains and colonies of them are said by Ogsten to be capable of locomotion, though this is not generally held. The rod-forms have often a mobile and a motionless stage, but some never move—*e. g.* B. anthracis, B. tuberculosis. In a few cases one or two cilia-like filaments have been found, but they seem to be connected with the cell-membrane (in the hay bacillus) rather than with the protoplasm, like true cilia; in others the mode in which motion is produced is unknown. Certain algæ, larger and higher in the scale than bacteria, move similarly, but have no cilia. Often no reason can be assigned for a change from motion to rest, or *vice versâ*. A good supply of oxygen seems to be connected with active motion of some forms.

All forms multiply by transverse division, which occurs in the rod-forms at right angles only to the long axis, but which in a round may take place in three directions at right angles to each other (*Sarcina*). The new cells formed by fission may at once separate from the parent, or they may remain united to each other end to end, forming chains of cocci (*Streptococci*) or long filaments of rods (*Leptothrix*), or lying side by side in more or less spherical colonies, bound together by a viscid intercellular substance—**zooglœa**—formed of swollen cell-membrane (Cohn) or of mycoprotein (in certain putrefactive bacteria—v. Nencki); or, again, when cocci divide regularly in two directions at right angles to each other, they give rise to square or oblong forms ("tablets"), and when in three directions to cubical figures (*Sarcina*). Naturally, zooglœæ form more readily upon moist solid than upon fluid substrata, separation of cells in the former being difficult, the amount of fluid being sufficient only to cause cell-membranes to swell up, but not to dissolve their adhesion to each other.

Upon the same substratum the zooglœa-form of a given bacterium is constant in mode of growth, and is often diagnostic of the organism; thus the hay bacillus in fluid media forms "skins" upon the surface, whilst the similar splenic-fever bacillus forms "swarms" (*i. e.* ill-defined zooglœa) at the bottom. Large aggregations of bacteria are always slimy, owing to the zooglœa. The "frog-spawn" coccus (*Leuconostoc*) may fill whole vats in sugar-factories, *Crenothrix Kühniana* and *Cladothrix dichotoma* may block water-pipes and cover reservoirs to a depth of several feet, and a species of Beggiatoa covers a large area of bottom in the Bay of Kiel, called the "dead" ground because fish avoid it; these few examples show how extensive may be the development of zooglœa.

The first sign of division is the appearance of a fine transverse line crossing the cell, continuous at its ends with the cell-membrane, and often at first imperceptible until stained with iodine—a point to be remembered in estimating the length of apparently single cells.

The time occupied in division has been variously given at from ten to thirty minutes; and, as the offspring proceed at once to divide like their parents, a single bacterium may, in twenty-four hours, give rise to a progeny which Cohn estimates at over sixteen millions.

But another method of multiplication is met with among the fission fungi—namely, the formation of spores; and, provisionally at least, these organisms have been divided into two groups: 1, **Endosporous**; and 2, **Arthrosporous.**

1. The **Endosporous group** consists at present of certain long rod-forms (**bacilli**) and some spiral forms, but it is more than likely that spores will be found in species in which they are not now known to occur. The spore forms as a minute point in the cell, which enlarges rapidly, and often attains maturity in a few hours. It is then a clear, round or oval, highly refracting body, which has evidently grown at the expense of the cell-contents; these gradually disappear. It is quite exceptional to find more than one spore in a single segment (De Bary). Specific differences are founded upon the form, size, and position of the spore in the cell.

Spore-formation frequently appears to be induced by exhaustion of the substratum, or perhaps by its becoming so charged with products of decomposition that vegetation is no longer possible; but this is not the sole or even an essential factor, as in some species vegetation and spore-formation may be going on together. The spores may develop in single rods, or these may grow into leptothrix-filaments

before spores form. Any cells in which viable spores do not develop die unless soon transplanted.

The spores are extremely resistant to unfavorable external conditions, owing, apparently, to the qualities of their fine limiting membrane. Under favorable conditions they germinate: their membrane swells and they lose their fine dark outline; the capsule splits and the new vegetative cell grows out in the direction of the long axis of the spore.

2. In the **Arthrosporous group** no spores are found within the cells, but certain cells, which may or may not be specially modified from the vegetative cells, become resting spores. As an example of the first variety the frog-spawn coccus may be chosen. It consists of chains of cells imbedded in zoogloea, and the zoogloea-forms are blended together into irregular masses as large as, or larger than, a hazelnut. When food is exhausted a cell here and there in the chains becomes larger than its fellows, all of which die. The large cell, if transplanted, germinates.

Of the second variety all micrococci and microbacteria are believed to furnish examples: the reproductive cells, so far as is known, do not differ morphologically from the vegetative.

Many bacteria are **monomorphic**—*i. e.* between their spore and their full development they exhibit only one form, that of their spore. Slight variation in the size and form of the cell is the only variation that such organisms present. Others are more or less **polymorphic**—*i. e.* in their developmental cycle we find spores, single rods (mobile or still), filaments, and zoogloea succeeding each other or more or less mixed up.

CONDITIONS OF LIFE.—Food.—Each variety of fungus seems to differ more or less from all others in its food-requirements, but all must be supplied with the materials from which they can obtain the elements of which they consist. These are carbon, hydrogen, nitrogen, phosphorus, sulphur, calcium, magnesium, and potassium. The first four are generally provided by carbohydrates and albuminoids, the rest by inorganic salts present in animal and vegetable tissues. Certain bacteria, however, can assimilate nitrogen and carbon from much less complex compounds than albumen and carbohydrates, as is shown by the growth of putrefactive organisms in Cohn's fluid (phosphate of potash, .5; sulphate of magnesia, 1; phosphate of lime, .05; tartrate of ammonia, 1; water, 100); to others

the more complex bodies are essential. Thus, beer-yeast will not grow unless glucose or some body convertible into it is present; the Bacillus tuberculosis grows best in blood-serum. It is probable that a fluid could be discovered and placed under such conditions for each fungus that it alone would grow in it. Raulin worked out the composition of such a fluid for a mould (Aspergillus niger), and proved the value of each constituent, no matter how small in quantity, by diminution in weight of the dried plant yielded by a certain quantity of the fluid on withdrawing the constituents.[1] Whereas, in nature, it is frequently stifled by other organisms more suited than itself to existing conditions, it here gets the upper hand of all. Very slight differences in the composition of the food-material may favor the growth of one organism rather than another. Nägeli says that in a neutral fluid containing sugar, in which were moulds, yeasts, and bacteria, only the latter flourished, causing lactic fermentation; the addition of half per cent. tartaric acid brought the yeasts to the fore, with production of alcohol; and the addition of 4–5 per cent. tartaric acid caused the moulds to develop. The **reaction** of the fluid has a marked influence in this respect; as a rule, acidity is unfavorable to the development of bacteria, alkalinity favorable—the reverse usually holding for yeasts and moulds. As showing what a very slight difference may suffice to prevent the growth of a bacterium, it will be remembered that Koch was unable to inoculate a field-mouse with an organism which always produced fatal septicæmia in a house-mouse (p. 457). Some similar difference would seem to exist between two men exposed to the poison of an acute specific, one of whom catches it, whilst the other does not. We must therefore bear in mind that a very slight, to us imperceptible, change in the metabolism of the body or of a part may enable organisms to flourish there, though previously unable to do so.

Water.—The presence of some water is essential to the development of all fungi, for it acts as the medium for conveying oxygen and food-substances into the cell. It is easy to add too much or too little for a given species, the moulds requiring less than the yeasts, and these, again, less than bacteria.

Nothing that is really dry ferments. Upon jam dried by addition of sugar moulds often grow; with less sugar or more water alcoholic fermentation is common, whilst with still more watery jam putrefaction may occur.

Desiccation destroys many (B. termo, cholera-spirillum) vegetative

[1] Duclaux, *Ferments et Maladies*, p. 43.

cells within a few days or hours; but many resist it for months, and spores of the endosporous group do so for years: it is impossible to say how long.

Oxygen.—Pasteur has divided fungi into **aërobic** and **anaërobic**, according as they require or do not require free oxygen as a life-condition. Certain fungi, as Aspergillus niger, B. anthracis, B. subtilis, M. aceti, die in the absence of free oxygen. Others are able to live both with and without it—at least for a considerable time—as Mucor racemosus (a mould), ordinary yeast, and Bacterium termo. Finally, the life-history of a few seems to be completely anaërobic; to B. amylobacter (butyric acid ferment) and Bacillus septicæmiæ of rabbits air is said by Pasteur to be not only unnecessary, but even fatal.

Oxygen under pressure may in the course of many days prevent vegetation of, and after months kill, even aërobic forms. Their spores also, according to Duclaux, retain their power of germinating much longer if oxygen is excluded: if true, this may partly explain the action of air as a disinfectant.

Temperature.—Each organism flourishes best at a particular temperature. All will grow less actively at temperatures above and below this point; but the range within which growth will take place may be very limited, as in B. tuberculosis, which is wholly parasitic upon warm-blooded animals. The general statement may be made with regard to bacteria that reproduction ceases in all these organisms at 5° C., and in many at a much higher point; but they do not necessarily die. Though rendered rigid and motionless (*rigor frigoris*), some are not killed by the greatest cold, and it is not certainly known that any are; the spore-bearing B. anthracis has been frozen in a fluid at —110° C. without injury. The maximum point is in most cases between 40° and 50° C. By further rise of temperature *rigor caloris* and death are induced—more easily in moist than in dry conditions, and much more easily in the adult than in the spore-form. The reaction and nature of the medium in which the germs are heated has a decided influence. Cocci and bacteria appear to be first affected by rise of temperature, then bacilli, and finally spores. Boiling, and indeed a much lower temperature (50°–60° C.) than 100° C., will kill the great majority of fungi; boiling continued for one or two hours will certainly destroy all non-spore-bearing organisms, but solutions containing spores may not be sterilized by 100° C. unless it is continued many hours. Thus Tyndall failed to sterilize a hay infusion by eight hours' boiling. This prolonged resistance of spore-containing

fluids to boiling is explained by supposing that fresh generations of adult organisms are developed after the boiling is over from spores able to resist 100° C. for a long time—a view supported by the fact that such fluids are sterilized by boiling for a few minutes only at intervals of several hours or a day.

Recently some vegetative forms have been found which withstand temperatures higher than those named. Duclaux found some bacilli (*Tyrothrix*) in cheese, the cells of which, in slightly alkaline fluid, were not destroyed by 100° C., but in an acid medium they were killed in a minute; the spores were not destroyed by 115° C. Other species of spore have been met with which have withstood a moist heat of even 130° C.

The dry spores of B. anthracis are not destroyed by less than three hours' exposure to 140° C.

Rest.—Fungi flourish better in a still medium than in one of which the particles are moving constantly: whilst B. anthracis divides actively in the blood-stream, other kinds (Micrococcus septicus) seem always to settle before multiplying.

These are the essentials to the **growth** of the plants which we are considering, but absence of growth does not necessarily mean death of the organism. If the conditions are unfavorable the cells will not develop, but they may not die. By making a sufficient change in any one of the above conditions the development, and consequently the action, of any given organism may be prevented. Use is constantly made of this fact to preserve substances which would otherwise ferment, and to destroy germs which have already gained entrance to them.

DISTRIBUTION OF BACTERIA IN NATURE.—Where are these microscopic vegetable organisms to be found? A putrid wound swarms with them. Whence do they come? 1. They may enter from the world external to the body; 2. They may exist in the healthy body, developing only under special circumstances; 3. They may be spontaneously generated under special circumstances from the elements of the tissues.

1. Earth, air, or water may be the habitat of germs external to the body.

(*a*) **Existence of Organisms in Earth.**—Portions of mould taken from the surface and dropped into a sterilized culture-fluid infallibly infect it. Cocci and bacilli are the forms which generally develop.

They are most numerous, and bacteria appear in the neighborhood of putrefaction. In winter Koch found that all organisms are absent at a depth of one meter in soil which has not been recently disturbed, which is not formed largely of decomposing material, and into which no unusual soakage of water occurs.

Not only the earth, but all other solids in contact with air, including the surfaces of animals, have organisms deposited upon them.

(*b*) **Existence of Organisms in Air.**—That dust contains much organic matter is easily shown by combustion, and cultivation proves that some of this is living. It has thus been found that spores of moulds are the commonest forms, then bacilli and their spores, whilst putrefactive organisms are much less common. Lister notes that the result of exposing pure urine for half an hour in his study in Edinburgh was the development of three moulds. Organisms of some kind exist in the air everywhere except away from all life—in mountains above the line of perpetual snow or on the ocean far removed from land and ships. Here a sterilized fluid would not ferment if left exposed till it dried. But with life, vegetable or animal, come germs, and they increase in number as the population increases and as putrescible material becomes more plentiful. Hesse found the air out of doors in Berlin to contain .1–.5 germs per liter, composed equally of moulds and bacteria; in a hospital ward he found 11.0 of bacteria and 1.0 of moulds; whilst in a cattle-stall at the Health Office he found on one occasion 58.0 of bacteria and 3.0 of moulds; upon another, 232.0 of bacteria and 28.0 of moulds. In some parts of London even it is possible to pour sterilized fluids from one flask into others with the result that but a small percentage will become turbid from the growth of germs; in other parts every flask will be infected. Precautions against such infection become necessary as density of population and imperfect ventilation increase; and it is obvious that in the hospitals of large towns such measures, to be successful, must be most stringent, for here putrefactive organisms will be comparatively numerous. A large number of the germs in air are incapable of development (Duclaux). We know that some fungi are killed by drying.

The air is kept supplied with organisms by currents which sweep them from the surfaces of objects over which they pass: the dust left as the final result of putrefactive processes is a fertile source of contamination. Perfectly still air becomes pure by subsidence of its germs.

(*c*) **Existence of Organisms in Water.**—All water except such as comes from a great depth (artesian wells) contains organisms. Rain-water sweeps the air, and infects the soil with the germs which it carries down. All surface-water is infected from the ground through which it soaks, and too often shallow wells are contaminated by sewage, etc. River-water is exposed to all possible sources of pollution. Miquel found 35 germs per cubic centimeter in rain-water caught as it fell near Paris; 62 in rain-water from the Vanne; 1400 in that from the Seine above, and 3200 from it below, Paris. It is scarcely necessary to add that unless the water contains sufficient organic matter to serve as food for the fungi, no multiplication will take place, and that sooner or later the germs will die, though perhaps not for many weeks. Many organisms in a sample of water render much organic impurity probable.

Microbacteria are the commonest forms in water, and their numbers would lead one to suppose that "clean" water would almost certainly infect a wound and set up fermentative changes in it. It is, we think, clearly best to avoid using it upon wounds; but it is equally evident that the danger of infection by water has been exaggerated, the tissues being usually able to deal with unexpected facility with the organisms ordinarily contained in it.

2. **Do Organisms Exist in the Living Body?**—They exist in large numbers on its external (skin) and internal (bronchial and alimentary) surfaces, which are in contact with air. On the skin they are most numerous on the hands—beneath the nails and in folds of skin about the nails; and on parts provided with hairs and large glands—*e. g.* the scalp, axilla, and perineum. These parts, therefore, require special care to effect their disinfection. Inhaled with the breath, they are found in the larger bronchi, but the smaller ones and alveoli are probably free, for Tyndall has shown that the complemental air is pure by its causing a non-luminous gap in an electric beam thrown across a dark room. Further proof lies in the fact that medical empyemata, communicating with the lung, generally remain free from putrefaction, whilst surgical empyemata, from external wound of the pleura, always putrefy.

With food and drink many living germs are carried into the alimentary canal. All kinds of fungi swarm in the mouth—cocci, bacteria, bacilli, and spirilla. They grow fewer toward the stomach, where the acid gastric juice is unfavorable to their development. Protected by their cell-membranes, some probably pass alive through

the stomach. At all events, organisms reappear in the duodenum before the food has become alkaline, and the pancreatic juice swarms with organisms after impure feeding. Indeed, the products of normal pancreatic digestion and those of ordinary putrefaction of albuminoids are practically the same. Throughout the whole intestine organisms occur, and in abnormal states of mucous membrane or in too prolonged retention of intestinal contents the fungi may multiply and excite irritation, and even poisoning, by the products of their action. Experience shows that after death putrefaction begins in the abdomen, spreading from the alimentary canal.

Lister has shown that a healthy urinary tract is free from organisms by obtaining pure urine directly from the urethra. This experiment has been widely confirmed.

But bacteria on the skin and mucous surfaces are *external* to the body proper—to the tissues. That organisms are found *in* the tissues in many diseases we shall shortly show; we have now to inquire whether they exist *in* the *healthy* tissues. The channels by which they may enter are a wound of the skin (for uninjured epidermis is impervious), the bronchial and the alimentary mucous membranes. In the lung they are probably taken up like carbon particles, carried to lymphatic glands, and thence perhaps into the blood. Many bacteria taken into the intestine pass out with the feces: five kinds have been cultivated and described as constantly present. The number of organisms passing through this mucous membrane varies with the number present in the food; it becomes very great when animals are fed on putrid material. Under these circumstances living organisms may be found in the urine, as will be the case also when a large quantity of washed putrefactive organisms is injected into the circulation (W. Roberts). Ordinarily, as above said, fresh human urine is sterile. Many germs, of course, are carried to tissues other than the kidney, and are found as yellowish masses in the capillaries: they are unable to obtain food in the healthy system, and die and disappear in two or three weeks, often much more rapidly. From the above data it is probable that under ordinary circumstances simple organisms enter the tissues of man in small quantity only, if at all, and that any which enter soon die and do not reach the urine alive. Attempts have been made upon the following plan to prove or disprove the presence of organisms in healthy tissues: Portions of healthy organs have been removed with such precautions and placed under such conditions as to prevent their contamination from any

extraneous source. The results have been contradictory. Mott and Horsley,[1] the latest writers on the subject, state that, with one exception out of twenty-one animals, organisms developed *when the preparations were incubated at* 37.5° C. They confirm previous observers by noting that coccus-forms precede rod-forms; that development of the latter from the former may be traced; that rods are generally found in kidney, less often in muscle, never in blood. The rapidity of development of organisms in *unincubated* specimens increased with rise of external temperature, but they do not state that such development was constant. Using the same animals, working in a room in which dust had subsided, and cleansing apparatus by heat only, Meissner kept organs in pure water free from change for two or three years. No mention is made of incubation, but it is fair to suppose that the specimens reached the same temperature as did Mott and Horsley's unincubated series. Watson Cheyne,[2] however, incubated organs in cucumber infusion with a negative result. There seems no reason to believe that development here was prevented by carbolic (the spray was used), for in a few cases organisms did appear, and they always developed when the gall-bladder was included or when bacteria had been injected twenty-four hours before death. It seems impossible entirely to reconcile the two sets of results; for the animals, their food, and the air which they breathed were probably much the same, and the balance of evidence seems to be distinctly in favor of the view that no living germs, putrefactive or other, are to be found as a rule in healthy tissues. But that the blood not uncommonly contains living pyogenic cocci is evident from the frequency with which inflammation and abscess result from bruises, not breaking the continuity of the epidermis (p. 277), especially in depressed states of system (p. 276). (For examples see references.) The cocci do not appear under healthy circumstances to leave the vessels: otherwise it would be impossible by antiseptic treatment (adapted to prevent the entry of living cocci *from without*) to prevent suppuration of wounds from causes reaching them *from within*.

The rarity with which any collection of putrescible fluid in the body undergoes putrescence, though the incubation-temperature is most suitable, and the certainty with which by care we can keep wounds "sweet," seem to be strongly against the existence of *putrefactive* fungi in healthy tissues. It is certain, however, that these may live for some hours after entry; so some "failures to preserve

[1] *Journ. of Physiol.*, vol. iii. No. 3. [2] *Trans. Path. Soc. Lond.*, 1879, p. 571.

portions of tissue" attributed to want of care may perhaps have been due to the presence in them of living germs at the time of their removal from the body. Again, if a suitable nidus be provided for the development of organisms they multiply and set up their characteristic decomposition. Thus Chauveau performed *bistournage* of a sheep's testis before and after the injection of septic bacteria in the blood.[1] In the latter case, in which the testis contained organisms, it broke down into a putrid fluid and excited much inflammation around: in the former the organ underwent fatty changes known as necrobiosis. This is the invariable course under normal conditions; and it shows, apparently, that organisms are not present normally in the sheep's testes.

Some organisms, however, seem capable of flourishing in tissues which are perfectly healthy—*e. g.* the poisons of the acute specifics and B. anthracis. Even here there is some very obscure difference between individuals of the same species or of closely-allied species, which renders some of them suitable media for the development of certain organisms, whilst others are unsuitable—*i. e.* more or less predisposition is required even where a species of animals is liable to a disease. Thus some people do not appear capable of contracting the acute specific fevers; children are more subject to acute specifics than adults; Algerian sheep are immune to splenic fever; young dogs are easily inoculated with the B. anthracis, but old ones are not. One great difficulty in the experimental study of the infective diseases of man is to find animals which are subject to them. So choice, indeed, are many of these organisms as to the nutritive and other conditions under which they will develop that they are satisfied only in certain tissues or fluids of the body: some multiply in the blood, others in lymph, some in bone (osteomyelitis), others in the cerebro-spinal meninges (epidemic cerebro-spinal meningitis), and so-forth.

To sum up these long paragraphs: Organisms in great variety, but in varying number, exist in air, water, earth, and on all objects exposed to air, on the skin, and on those mucous surfaces which are in contact with air. Organisms probably pass constantly through the pulmonary and intestinal mucous membranes, but in small number; and such as ordinarily thus enter the tissues are unable to develop so long as the latter are healthy. The life of such fungi among the tissues is short. It seems to be a very rare thing for them to reach the urine alive. Occasionally an organism which is not universally pres-

[1] *Nécrobiose et Gangrène.*

ent and which can develop in living tissues enters the tissues. The recipient of such organisms is in more or less danger of disease. The great majority of mankind afford a suitable nidus for the development of some fungi; thus few are immune to the vaccine virus. All organisms perhaps flourish best in tissues of which the vitality is impaired; some probably cannot develop unless this is the case; and still another group cannot multiply in living tissues at all. Two great divisions (clinical) of organisms are thus obtained: 1. The **Pathogenic,** or those which can invade and multiply in living tissues, giving rise almost invariably to disease; 2. The **Non-Pathogenic** or **Simple,** which can develop only in dead tissue, and are therefore found chiefly on the surface of the body, where sloughs and discharges are common. Perhaps the most important of these are the Bacterium termo and other causes of putrid decomposition. It is a very rare occurrence for these fungi to find their way alive to an internal slough or putrescible effusion, as they did in Chauveau's experiment.

3. **Spontaneous Generation.**—The possibility of organisms originating *de novo* from the molecules of decomposing tissues must be mentioned, but cannot be discussed. The great majority of observers are agreed that there is no evidence of its occurrence at the present day. They hold that if a fluid or moist solid be thoroughly sterilized, and placed under such conditions that no organisms can enter from without, no organisms will ever develop.

We conclude, therefore, that organisms found in a putrid wound have entered it *from without*, and that the same is true of fungi found in pathological lesions within the tissues, the organisms having entered by a wound or mucous surface. For the present, at least, we must adhere to the belief that neither living organisms nor their spores exist normally in the tissues; and that they are never eliminated alive by an excretory organ or by a wound.

This is of fundamental importance in surgery. If organisms could enter a wound from the side of the tissues, aseptic treatment would be impossible. As it is, we are sure that if we allow no loophole for the entry of germs from without, our wounds will remain free from ferment-processes. Patients are thus saved from the danger of septic intoxication (p. 456), from septic infection (p. 457), pyæmia (p. 459), and other infective diseases. Attention to general hygiene is the only way at present known to prevent invasion of the system by fungi which cause "medical" diseases. Once organisms have gained access to the tissues, it is extremely difficult to destroy them without also

destroying the tissues. Improvement of the general health probably often enables the tissue-elements successfully to resist invasion.

ORGANISMS IN LIVING TISSUES: LIFE OR DEATH?—MODES OF SPREADING—EFFECTS.—It by no means follows that germs which have actually entered the tissues will multiply and give rise to disease. Just as in the case of infective inflammations, so in all other infective diseases, we have always to remember that *there are two factors in the production of disease*—the germs on the one hand, and the tissues upon the other (see p. 271, *et seq.*); and at p. 284 we have stated what is known of the manner in which the battle, when ending in the victory of the tissues, is waged. We may recapitulate very shortly the conditions which influence these two factors—increasing or diminishing the power of the organisms or acting similarly upon the resisting power of the tissues.

(1) **Arrest of an organism** is absolutely necessary before it can by its metabolism produce local irritation and inflammation, for if its products are poured into the circulating blood they become too dilute to do harm. But such arrest is not necessary for organisms which, like that of septic infection of mice, act by pouring into the blood poisons which cause fever and other symptoms. We may here remember, however, that all of these organisms multiply more rapidly, and some only, when **at rest.**

Arrest of circulating germs may be produced in man by embolism or thrombosis, by injury leading to extravasation, by migration from a vessel and subsequent death of a leucocyte bearing in its interior one or more germs; which will occur most easily in parts in which the vessels are distended and the circulation slow (venous congestion). It is conceivable that a germ might escape unaided from a vessel under these circumstances, just as a red corpuscle does.

(2) The **Predisposition of the tissues to infective diseases** may be increased either generally or locally. **General depression** of resisting power may arise from general poisoning of various kinds, privation, faulty hygienic circumstances, acute and chronic diseases, either general or manifestly affecting the body as a whole. Bright's disease and diabetes in some unknown way render the conditions favorable for invasion of the skin by pyogenic cocci (diffuse cellulitis, boils, and carbuncles). The causes of **local depression** are detailed at p. 277; and there is nothing to add to what is there said on the effects of (3) the **seat of inoculation** and **the anatomical arrange-**

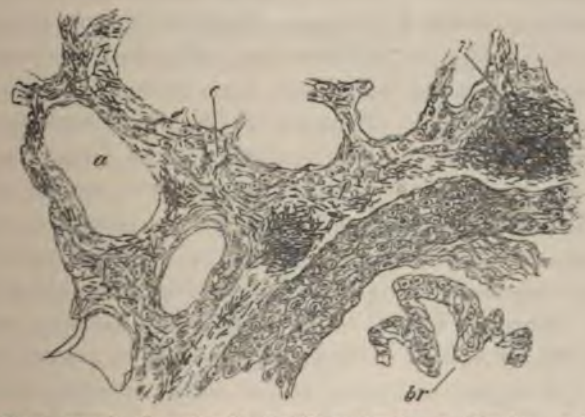
ment of the part; (4) the species; and (5) the number of the organisms inoculated; (6) of variation in the virulence of the organisms; (7) of concurrent growth with other organisms of that which is specially under consideration; and lastly (8) of local and seasonal conditions.

Supposing the conditions to be favorable to their growth, pathogenic fungi differ much in the course which they pursue. Some remain about the spot at which they first settled; others spread by continuity of tissue with all degrees of rapidity, or pass along lymphatics, settling in them here and there, or not being again arrested until the nearest glands are reached; or they may at once enter the circulation and be carried all over the body. Some species remain and multiply in the blood, and may be seen in the plasmatic zones of veins in translucent parts; others require to be again deposited, and at a spot predisposed to receive them: doubtless disease is often escaped by the deposit of germs at spots other than weak ones.

Spread in the tissues always occurs along lines of least resistance, as is best seen when the cornea is inoculated with fungi; they then run along the cell and lymph-spaces, forming a characteristic "Pilzfigur."

Effects.—These are chiefly (1) general poisoning (of which fever

FIG. 166.



Mouse's Lung, vessels plugged with Bacilli anthracis. *a*. Alveolus. *v*. Vein full of bacilli. *c*. Capillary, also full. *br*. Bronchus. × 500, slightly reduced.

is by far the commonest result), due to the passing of pyrogenous substances into the blood; and (2) local irritation and consequent inflammation. Germs often act both locally and generally. Para-

sitic fungi will produce some effect by **abstraction of nourishment** from their host, and perhaps also by **plugging a large number of the vessels** of some important organ, as the lung. The accompanying figure (Fig. 166), showing the bacillus of splenic fever in the vessels of a mouse's lung, gives an idea of the extent to which this process may be carried. The specimen was kindly given by Mr. Horsley.

SPECIFIC CLASSIFICATION OF BACTERIA.—Authorities differ as to whether this is possible. Some hold that all forms are merely developmental stages of one (Coccobacteria septica, Billroth) or of a few undetermined forms (Nägeli), change of form being due to change in external conditions, and being possibly accompanied by change in physiological action; others (Cohn, Koch, and most recent writers) believe that distinct species are numerous. Provisionally they divide the whole class of Schizomycetes into the two groups—**Endosporous** and **Arthrosporous** (p. 471)—according to their mode of reproduction. For generic differences they turn to morphology, and obtain—1. Cocci (round and oval forms); 2. Microbacteria (rods of which the length is not more than twice their breadth); 3. Desmobacteria or Bacilli (rods of which the length is more than twice their breadth); and 4. Spirobacteria (spiral forms); but Cohn, to whom this classification is due, put it forward as provisional, being uncertain whether these form-genera were or were not natural genera. Specific differences are established by minor differences in form, such as variation in size and form of the elementary cells, their macroscopic and microscopic group-forms, their effects upon various substrata, including the bodies of animals. To obtain satisfactory evidence upon these points it is *absolutely necessary to watch* a given form pass through its *whole developmental cycle* from spore to spore, and to note carefully the different forms it assumes, their natural succession, variations in their size, and so forth, and to do this upon various substrata and under any conditions which may be supposed to be capable of inducing variation. Wherever this laborious investigation has been carried out no reason has been found to doubt the existence of distinct species of bacteria. And just as among higher forms varieties, species, and even genera, have been grouped together at first until the differentiating points were discovered, so, doubtless, is it with bacteria: the number of known species will increase largely. Two coccus-forms may appear to be exactly the same until inoculated upon some particular animal, when one will be found to be pathogenic, the other

not. As analogous to this among higher structures, Cohn points to the close naked-eye and microscopic resemblance between the sweet and bitter almond, the physiological actions of which are so very different; and Virchow in the same sense alludes to the impossibility of distinguishing between the cells of the early embryo, though their potentialities are so various.

Difficulty naturally arose in early times from imperfection in the culture-methods, from inappreciation (as De Bary forcibly points out) of the absolute necessity of seeing the development of any given form throughout its whole cycle, and, lastly, from the polymorphism of certain forms which has before been alluded to. Koch's solid culture-ground fixed the organisms under examination, and added enormously to the ease and certainty with which pure cultures were obtained: more exact work followed; and as it was found that the various developmental stages of polymorphous bacteria were constant in appearance and order of succession, they were obviously no more disqualified by their polymorphism from specific classification than was the frog on account of its tadpole stage.

In support of the view advanced by Billroth and Nägeli the following have been the chief arguments:

1st. That in successive cultivations, especially in different media, the forms developed have varied greatly from the original, assuming in succession the shapes characteristic of Cohn's orders, and at the same time their physiological activity has changed equally. This is, of course, a direct contradiction of Koch's experience, and *may* be true; but it must be remembered that the difficulty of obtaining pure cultivations in fluid media is great, and that the method employed (successive cultivation) is one in which error is easy. In fact, it is far easier to fail than to succeed; so the suspicion that the cultivations were never pure or became contaminated by other organisms arises.

2dly. Different forms of bacteria are found taking part in the same decomposition (*e. g.* putrefaction). This shows simply that several different organisms are capable of living in the same fluid; the process is a complex one, and the products are the result of the life-actions of different forms; it does not show that different forms develop from one species.

3dly. The same form may be found associated with the most different chemical changes. Thus, micrococci, indistinguishable from each other by form or size, occur in relation with diphtheria, erysipelas, smallpox, pyæmia, infective osteomyelitis, and many other diseases.

They cannot be the same if they are the causes of these maladies: but that similar forms may be specifically distinguished by their physiological activities has already been shown (p. 484).

4thly. Coze and Feltz, Davaine, and others, produced an artificial septicæmia by injecting putrid fluids, containing many forms of bacteria, into rabbits, and found that the virus increased as the disease was transmitted from animal to animal; so that in the twenty-fifth transmission of a series Davaine produced fatal septicæmia with one trillionth of the original dose of one drop. But this apparent increase in virulence was due to neglect of a control-experiment made by taking the smallest quantity possible at an early stage. Davaine himself thus found that no increase of virulence occurred after the second or third generation; and Koch shows that even this was due to greater purity of the organism inoculated, forms other than that specific to the disease having rapidly diminished, whilst the specific one increased and multiplied. Similar increase in physiological activity produced by cultivation has been alleged to occur in other organisms, and has been similarly explained.

More recently it has been found that the virulence of "attenuated" virus may be restored by suitable cultivation, and that an exceptional virulence may be imparted to B. anthracis by the addition of a little lactic acid and sugar to its culture-ground.

This argument, as a whole, is beside the mark; for variation in intensity of virulence, accompanied by no morphological change, would not constitute any difficulty in specific classification—a remark which must be extended to the following paragraph also.

5thly. Starting from Jenner's discovery of vaccination against smallpox, Pasteur succeeded first in so mitigating or "attenuating" the virus of chicken cholera by leaving the organisms in chicken-broth exposed to air for eight to ten months that when inoculated upon fowl it caused only a slight illness and left the creature protected for about a year. Repeated inoculation is more certain and lasting in its effects. Similarly, by cultivating B. anthracis for twenty days at 42°–43° C., and using the vaccine for repeated inoculations upon sheep and cattle, these were rendered immune to the spontaneous disease and to the action of the virulent virus. After much controversy the possibility of this "attenuation" of a virus is fully established; there is, however, still some doubt as to the value of vaccination against splenic fever, Koch, for instance, maintaining that to be of any use the vaccine must be so strong that some animals, and perhaps very

many, will die of the disease induced. The attenuation of splenic-fever virus has been brought about in other ways—by cultivation in air under a pressure of eight atmospheres (one to two drops said to render cattle immune for twelve months—Chauveau), by the addition of small quantities of antiseptics to the substratum, or by the passage of the virus through the bodies of certain animals. Klein failed with Pasteur's vaccine to protect rodents: they seemed to have no immunity; if the vaccine acted at all it caused splenic fever.

The attenuation is not accompanied by any morphological change: the virus "breeds true," and its virulence may be restored at any time. So, as Baumgarten puts it, mitigation of virulence is no better ground for depriving a bacterium of its specific character than would be the extraction of the teeth of a poisonous snake a reason for regarding it as changed into a non-poisonous.

6thly. Buchner stated that by cultivating the non-pathogenic hay-bacillus in meat-infusions and in unsterilized blood he made it "wild," and converted it into B. anthracis: and that by a converse process he converted B. anthracis into B. subtilis. The experiments have been repeated by Koch and others with a negative result. There are distinct morphological differences between the two bacilli, of which Buchner does not seem to have been aware; and inability to distinguish certainly between the two species constitutes a radical flaw in the investigation.

This is the experimental evidence as to the **mutability of bacteria.** At present the balance is most decidedly against it, but Koch himself recognizes that his experiments do not prove its *impossibility.* Like all other organisms, these unicellular beings must have more or less power of adapting themselves to altered surroundings, and they are modified by their environment: they may grow more or less rapidly, their cells may be larger or smaller, may separate early or remain united in strings, threads, rounded heaps, or zooglœa; on poor substrata the developmental cycle of a polymorphous form may be incomplete, or the cells of a monomorphous form may be stunted and irregular, or abnormal ("involution" forms, Nägeli) forms may appear; they may be rendered more or less virulent. But Koch's observations of various bacteria, often extending over years, suffice to show that all he dealt with preserved unaltered through long series of cultivations their inherited characteristics. Once the life-history of a species (monomorphous or polymorphous) was known, no important departure from its various stages was ever noted: [illegible] the con-

cus of erysipelas has never been seen to grow into a bacillus or a spirillum.

Looked at from the clinical point of view, every one feels that the best-marked group of infective diseases—the specific fevers—must have an unvarying, a specific, cause. Most observers believe that these diseases never arise except by infection from a previous case. Assuming the virus to be a fungus, they admit that it must at some time have acquired the physiological action which enables it to produce a certain disease; but they hold that there is no evidence that harmless fungi do at the present time ever acquire such powers. Isolated communities remain free from such diseases for centuries until a case is introduced among them; then it spreads with the utmost rapidity. In 1520 a negro covered with smallpox pustules was landed on the Mexican coast, where the disease was not yet known: three and a half millions are said to have died of it. In 1846 measles was introduced from Copenhagen into the Faroe Islands, and almost every one suffered. Similar facts concerning other acute specifics are given by Sir T. Watson in the *Nineteenth Century*, No. 3. Murchison and others believed that typhus and typhoid might originate *de novo*, being filth-begotten; but the conditions of life in slave-ships and Arctic winter-houses are as unsanitary as ever they were in our jails when typhus was endemic in them, yet no typhus occurs. As to the origin of typhoid from sewer-gas, continental towns show that exhalations of it may be intense and prolonged without ever generating typhoid.

The poison of the most infectious diseases has obviously so great a power of spread by air, food, clothing, etc. that it is almost impossible to find a case in which the possibility of infection from a previous case cannot be shown. The less infectious kinds have therefore been turned to by the advocates of the *de novo* origin. Many cases of supposed spontaneous origin of diphtheria are recorded, and an urethral discharge like gonorrhœa in symptoms and communicability may, it is said, be contracted from a woman suffering from any foul discharge not gonorrhœal. But it is quite possible that urethral discharges may be excited by infective irritants other than the gonorrhœal poison. With regard to the so-called "hospital diseases"—pyæmia, septicæmia, hospital gangrene—there is, perhaps, evidence of some change from non-pathogenic to pathogenic organisms. How otherwise is it to be explained that when a new building, which has never before contained wounded, is taken in time of war as a hospital,

these diseases break out so soon as crowding of the wounded reaches a certain point, whilst they do not attack patients in tents close by? Can we suppose that the specific causes were present in the building? or do not the facts tempt to the belief that ordinary bacteria acquire pathogenic properties by cultivation under the conditions brought about by overcrowding of the wounded? The state of atmosphere produced in the building would seem to be analogous to the "epidemic influence," that influence which causes infective diseases every now and again to become widely epidemic. From the clinical standpoint, therefore, it would seem that but little evidence is forthcoming in favor of the mutability of bacteria; but the question must be regarded as still *sub judice*.

It will be seen that by origin *de novo* a germ-theorist understands not the spontaneous development of an organism, but the acquisition under suitable cultivation of pathogenic properties by a non-pathogenic fungus.

VARIETIES AND ETIOLOGY OF THE INFECTIVE DISEASES.—The acute specific diseases, to which allusion has so often been made, are now regarded as forming a class in the much larger group of **Infective Diseases.** These may be defined as diseases due to the action of a poison or virus which has the power of invading and multiplying in living tissues. They may be **local** or **general**—*i. e.* the virus may be able only to invade the tissues for a greater or less distance about its point of entry, or it may be able, either directly by multiplying in the blood or indirectly by throwing into it the products of its action in the tissues, to excite the tissues in general to increased metabolism (fever), and perhaps to lodge in other tissues and excite fresh foci of disease.

These diseases are divided according to certain characteristics of the virus:

1. **Contagious** or **Infectious.**—These are communicable only from individual to individual; the poison runs its whole course of development in the body. Scarlet fever, measles, and smallpox are examples of the acute general variety. They are frequently epidemic. Gonorrhœa and soft chancre are examples of local contagious diseases.

Strictly speaking, "contagious" should be a term reserved to indicate communicable only by actual coarse contact with the poison, either upon some morbid surface or upon something which has been in contact with such a surface. The term "infectious" may be

applied to diseases which are communicable without such apparent contact—the individual is struck, as it were, from a distance.

2. **Miasmatic.**—These are endemic diseases, of which malarial fever is the type. This disease is not communicable from man to man; the poison which causes it develops outside the body, having no relation to a previous case of ague.

3. **Contagio-miasmatic.**—In this class are placed certain diseases which seem to be derived always from a previous case of the disease, but not directly; the poison has to go through some change external to the body. The usual examples are typhoid and cholera. There is doubt as to what constitutes the peculiarity of this group. The hypothesis of an essential change taking place external to the body originated with the Munich school. But Pettenkofer has abandoned it, and thinks that these diseases differ from the miasmatic simply in being transportable by man from their seat or seats of origin.

4. There would seem to be another set of diseases—**septic**—the poisons of which may be derived from many putrid infusions. When the disease has once been started in this way, it can be transmitted directly from individual to individual indefinitely.

It will be remembered that, having pointed out the analogy which exists between fermentation and infective disease, we considered the views which have been put forward as to the etiology of fermentation, and concluded that the germ-theory was almost certainly the true one. It seems impossible to furnish absolute proof of it, for it is impossible to cleanse the germs so thoroughly as to be sure that no particles in a state of "motor decay" are added with them to a test-fluid. The facts, however, that the particles in a state of motor decay have never been demonstrated apart from organisms, and that the properties of the cause of fermentation appeared to be those of a living thing, render it, as has been said, almost certain that organisms stand to the process of fermentation as cause to effect. There is, therefore, on the strength of the above analogy, a *primâ facie* case in favor of the germ-theory as applied to the infective diseases. And it will be found upon examination of the evidence yielded by actual observation of these diseases, and by experiments upon animals, that the demonstration of the causal relationship of organisms to them is in some cases as complete as it is in the case of fermentation, although in the great majority the proof is still more or less doubtful.

To prove that a micro-organism is the cause of a disease it is necessary—

1. To find the same organism, recognizable by its form, mode of growth, or product, constantly associated with the disease, at least in its earlier stages, and in sufficient numbers to account for the symptoms.

2. To make "pure" cultivations of this organism through several generations, and when it may reasonably be supposed that all else taken from the animal which yielded the virus has disappeared, to inoculate other animals with the cultivated organism and thus to produce the disease.

3. To show that the organism is present in the tissues of successfully inoculated animals in such numbers and with such a distribution as to account for the disease.

The demonstration of a *well-characterized* organism in *constant* association with a disease is now by many taken as almost equivalent to proof that it is the cause of the morbid process. For it is in most cases impossible to experiment on man, and frequently no animal can be found which suffers from the disease under investigation. Consequently, the proof cannot be carried beyond the first stage. This, however, is no proof at all to those who believe that under certain circumstances a certain form of organism will develop spontaneously; nor is it satisfactory to others who think that when a nidus favorable to a certain organism exists, that organism is sure to drop into it.

The amount of patience and skill necessary to carry on an investigation of the above kind can be appreciated only by those who have worked at the subject. They are not surprised that so few diseases have been thoroughly investigated. In the case of man the difficulty of obtaining material in the early stages of diseases and sufficiently soon after death must also be taken into account. Until quite recently, too, the methods employed were wholly inadequate to the discovery of many kinds of fungi. At first there was unaided microscopic examination only, and with inferior glasses; the detection of all fungi under these circumstances was very difficult, and often impossible. A considerable step was made when v. Recklinghausen in 1871 pointed out the uniform size and the resisting power of micrococci against dilute acids and alkalies and glycerin as a means of diagnosis between them and fatty and albuminoid particles. But progress has been much more rapid since the introduction by Abbe of a powerful substage condenser, by Weigert of the aniline dyes as stains for organisms, and by Koch of many improvements in the mode

of examining specimens and of carrying on pure cultivations. Some details of these processes will be given later.

THE SCHIZOMYCETES.

We shall now, adopting Cohn's classification, give the orders, genera, and some of the species of the Schizomycetes, and state the grounds for believing that certain of them are causally associated with disease.

Order 1. **SPHÆROBACTERIA or MICROCOCCI.** — These are round or oval cells, generally .5 to 2μ in diameter, single, in pairs (*diplococci*), or in chains (*streptococci*) of four to twenty cocci (sometimes two hundred or three hundred), which may be straight or wavy, in groups like bunches of grapes (*staphylococci*), in colonies and zooglœa-masses. The chains only seem sometimes to have slow spontaneous movement. They differ among themselves in form, size, mode of grouping, and physiological action, and thus are established genera and species.

There are two genera—Micrococcus and Sarcina.

1. **Genus Micrococcus.**—Cohn arranges the species of Micrococcus in three groups—pigment-forming, fermentative, and pathogenic.

(*a.*) **Pigment-forming.**—Uncolored themselves, they form in contact with air slimy films of various colors. They are frequently seen on bits of boiled potato. The color does not vary with the soil, but is specific to each form. The species are—M. prodigiosus (red or blood-portent), the cause of the "bleeding" host: M. luteus, aurantiacus, chlorinus, cyaneus—the cause of blue pus—and violaceous.

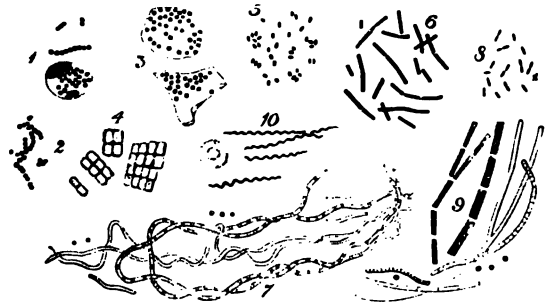
(*b.*) **Fermentative.**—M. ureæ, *a* cause of the ammoniacal fermentation of urine, which it enters from the air. Urine obtained pure and exposed only to pure air will keep acid for years. The change effected in the transformation of urea into ammonic carbonate is said to be due to the action of an unformed ferment secreted by M. ureæ,[1] which must be indiffusible, for the urine in an excised bladder does not putrefy even if placed in putrid urine. The change often occurs in urine contained in the living bladder, and may extend up to the pelvis of the kidneys with the most fatal results (suppurative nephritis, p. 401). M. ureæ is rather large (2μ), and occurs singly or in chains.

Leube has demonstrated the existence of four other distinct bac-

[1] Musculus, *Compt. Rend.*, vol. lxxviii.

teria producing the same effect on urea. But these and M. ureæ are aërobic, and are therefore unlikely to be the causes of putrefaction of urine in the bladder. Miquel has discovered a delicate bacillus having a similar action which is anaërobic.

FIG. 167.



1. Micrococci from an Acute Abscess, streptococci free, staphylococci in a pus-cell. 2. Streptococci from secondary suppuration in elbow (puerperal fever; lent by Mr. Horsley). 3. Micrococci from gonorrhœal pus in cells. 4. Sarcina ventriculi—"tablets," no forms of three dimensions being shown. 5. Bacterium termo. 6. Bacillus anthracis, from the blood of mouse (lent by Mr. Horsley). 7. Chains from cultivation of B. anthracis; some bearing spores (after Duclaux). 8. Bacillus of typhoid, from a mesenteric gland (lent by Dr. Gibbes). 9. B. malariæ: dichotomous division, parietal spore-formation, jointed and unjointed threads, which appear in cultures and fine spores; × one-twelfth, oil-immersion, Zeiss (after Klebs and Tommasi Crudeli). 10. Spirilla of relapsing fever and red corpuscle (after Vandyke Carter). All × 500 except B. malariæ.

(*c.*) **Pathogenic.**—The absence of distinctive form is a great difficulty in the carrying on of "pure" cultivations and in the demonstration that a specific coccus is the cause of a disease. Cocci are more frequently associated with diseases than any other form of fungus.

Acute Suppuration.—We have already (p. 282) shown that acute suppuration, in practice at all events, is due invariably to the action of certain organisms, of which the chief are the Staphylococcus pyogenes aureus, Staphylococcus pyogenes albus, and Streptococcus pyogenes (Fig. 167). We should have noted that the earliest proof of this constant and causal relation between cocci and acute abscess was afforded by Ogston,[1] who obtained pure cultivations of the cocci in eggs and successfully inoculated animals. It is interesting to note that some animals, even of the same litter, proved much more resistant than others.

In some cases well-marked **septicæmia** occurred, the symptoms in mice being such as were described by Koch. Micrococci were then found in the blood, though never in very large numbers apparently.

[1] *Brit. Med. Journ.*, p. 369, vol. i., 1881.

Again, in **metastatic pyæmia** micrococci in numbers are found in the secondary foci (Rindfleisch, v. Recklinghausen, and many others). It has been shown that the unhealthiness of the wound is in proportion to the number of zooglœa-masses on its surface, and the severity of the disease to the number of cocci in the blood (Birch-Hirschfeld): the cocci have been traced from the wound into connective-tissue interspaces and into a vein (Klebs). They are present in all clots undergoing infective softening.

Ogston therefore concluded that septicæmia, pyæmia, and septico-pyæmia are only symptoms of micrococcus poisoning. They are simply secondary phenomena dependent on local centres of micrococcus growth: there is no clear line between these diseases and a simple abscess.

Rosenbach[1] examined 6 cases of metastatic pyæmia and found the Streptococcus pyogenes in 5, in 2 of which it was accompanied by a smaller number of Staphylococcus pyogenes aureus. In 1 case—the only one which recovered—the latter coccus occurred alone. Again, in 15 cases of acute osteomyelitis which may give rise to pyæmia before the abscess is opened, Rosenbach found staphylococcus alone in 12 cases, in 1 mixed with Staphylococcus p. aureus albus, and in 1 with Streptococcus pyogenes: in 1 case he found Staphylococcus pyogenes albus. His cultivations and inoculations of animals go far to support Ogston's views.

As to **acute osteomyelitis**, Rosenbach, as above said, demonstrated that the organism previously cultivated and studied by Löffler, Becher, and Krause was really the Staphylococcus p. aureus in the great majority of cases; and he was further able to support Löffler in his statement that Staphylococcus p. aureus when injected into the veins of animals whose bones had been bruised or fractured caused acute osteomyelitis; and this whether the source of the organism employed was a case of osteomyelitis or a boil.

Spreading traumatic gangrene, again, according to both Ogston and Rosenbach, would seem often to be due to the Streptococcus pyogenes. Ogston found that injections of Staphylococcus might cause similar gangrene of the skin in animals. It will be remembered that Koch[2] induced a spreading gangrene in rabbits by injections of a little putrid blood, and here a streptococcus only developed. In two cases of spreading traumatic gangrene in which emphysema was a

[1] *Micro-parasites in Disease*, New Syd. Soc. Trans.

[2] *Wundinfectionskrankheiten.*

marked feature Rosenbach found a peculiar bacillus, very few cocci being present.

Lastly, the above coccus-forms may give rise to **inflammation stopping short even of suppuration**, the streptococcus being associated with the *more diffuse* varieties. The evidence we have of the infective nature of papillary and ulcerative endocarditis is given at pp. 374, 375.

The circumstances under which these apparently very different results are obtained are unknown; but surmise suggests that idiosyncrasy, attenuation of the virus, number of organisms inoculated, or a continuous supply from a wound, or the anatomical structure of the part infected (loose or dense), may have some controlling influence.

Erysipelas.—Micrococci have often been described in erysipelatous skin, especially at the spreading edge; v. Recklinghausen and Lukomsky[1] showed that they occupied the lymphatic channels and spread along them (hence the name—infective capillary lymphangitis). Orth produced typical erysipelas in a rabbit by subcutaneous injection of the fluid from an erysipelatous bulla; with œdema fluid from this animal he successfully inoculated another; the fluid and affected skin contained cocci in large numbers. Orth cultivated the fungus, and produced erysipelas by injecting it. Koch[2] figured streptococci in the skin-lymphatics, and was aware of their constant presence here. In 1881, Fehleisen[3] independently found numerous cocci in chains constantly present in bits of skin excised from the *spreading edge* of an erysipelas rash; they lay in the *lymphatics*, chiefly of the *superficial part* of the corium, and in the subcutaneous fatty tissue, never in blood-vessels. They had excited round-celled infiltration about them. The cocci were cultivated upon gelatin through fourteen generations in two months; eight out of nine rabbits now inoculated suffered from the disease; six out of seven inoculations upon man were equally successful. The incubation was fifteen to sixty hours; then followed rigors, fever, and typical rash. The disease was severe in two cases. Immunity, if conferred at all, lasts less than two months; 3 per cent. solution of carbolic acid, 1 per cent. of perchloride of mercury, stopped the growth of the fungus.

Fehleisen stated that the Streptococcus erysipelatis presented distinct though slight differences from the Streptococcus pyogenes, and

[1] *Virch. Arch.*, vol. lx. p. 418.
[2] *Mitth. a. d. Königl. Gesundheitsamt.*, vol. i. 1881.
[3] *D. Ætiologie des Erysipels.*

that it never caused suppuration, abscess with erysipelas being due to a mixed infection. The majority of recent writers upon the question, including among them men of much experience, have failed to detect morphological or physiological differences, and many are therefore inclined to think that the two organisms are identical, and that the point of inoculation, attenuation of the virus, and such-like conditions must determine whether erysipelas or diffuse subcutaneous suppuration shall occur in any given case. The clinical differences between the two diseases would seem to warrant hesitation in accepting this view until it has been proved that S. erysipelatis (*i. e.* taken from a case of undoubted erysipelas) causes diffuse suppuration, and, on the other hand, that S. pyogenes from an acute abscess gives rise to erysipelas. No case of erysipelas from inoculation of a wound with pus containing streptococci seems to have been recorded, but Rosenbach saw a dense inflammatory mass (practically a "boil") develop round the opening into an empyema containing Streptococcus pyogenes.

Gonorrhœa. — Neisser in 1878 described a large micrococcus (Staphylococcus gonorrhœæ, gonococcus, Fig. 167, $_3$) peculiar to this disease, by "facets" or flattenings on the surfaces of contact (now known to occur in other rapidly-multiplying cocci), distinguished from ordinary cocci by its size, by the equidistance, about equal to the diameter of a coccus, between the individuals in the groups, and by their occurrence upon the surfaces of, and in, cells—rarely free; and he used it as a means of diagnosing gonorrhœal discharges from the urethra, eye, etc. The cause of the separation of the cocci is swelling of their capsules (De Bary). The number of cells affected is always relatively small, and varies in different cases. The coccus is cultivated with much difficulty. Neisser failed, but culture is said to have been successfully carried out by Bockhardt.[1] He injected a fourth cultivation into the urethra of a general paralytic and produced a purulent discharge. The man died of pneumonia ten days later, and an examination of the urethra led Bockhardt to believe that the cocci probably pass through the epithelium into the lymphatics of the fossa navicularis, where they excite lively inflammation. They enter into white corpuscles, and pass with them into blood-vessels, where they die; or they come away in the pus.

Since then Hausmann has cultivated the gonococcus from gonorrhœal conjunctivitis, and Bumm,[2] whose work is the best on the

[1] *Sitz. Bericht. d. Phys. Med. Gesellsch.*, Würzburg, 1882.

[2] *Die Mikro-organismen der gonorrhoischen Schleimhauterkrankungen*, 1887.

subject, from the urethra. Bumm succeeded in cultivating only upon solidified blood-serum; he inoculated a second and a twentieth culture upon the female urethra, causing typical gonorrhœa in each case.

With regard to complications: the occurrence of suppurative lymph-adenitis (bubo), which is unusual in gonorrhœa, is said to be due to infection of the gland by ordinary pyogenic organisms, the urethra in these cases being the seat of a mixed infection. The gonococcus injected into subcutaneous tissue does not cause suppuration, but disappears in twenty-four to thirty-six hours.

The evidence as to the presence of the gonococcus in joints, the seats of gonorrhœal arthritis, is contradictory: perhaps anthritis also is the result of a mixed infection, but we may note that it is quite unusual for gonorrhœal joints to suppurate.

The gonococcus is incapable of multiplying external to the body, except under the very special conditions of a culture. Its resisting power is feeble and it soon perishes. Otherwise, considering the great frequency of the disease, infection in any manner than by contact would surely sometimes arise.

Pneumonia.—Klebs described a micrococcus as present in pneumonia,[1] and was confirmed by Koch[2] and Friedländer,[3] who demonstrated the almost constant presence of the organisms in great numbers in the early stages, not only in the exudation, but also in the lymphatics of the lung and in the fluid of any pleurisy or pericarditis which may be present. These fluids, he says, may be turbid from the organisms, which are far more numerous than leucocytes. The cocci are oval or shortly rod-shaped; they are contained in oval or elliptical capsules with rounded ends. Two, four, or even more cocci may be found in these capsules; sometimes a capsule with one or two clear spots in it or homogeneous is found (cocci probably dead). The capsule is seldom less broad than the coccus, and may be two to four times as broad. It is dissolved by alkalies and water, contracted by acetic acid (like mucin), is present only in the lung, being scarcely or not at all developed in cultures, and is best stained in cover-glass preparations by two to three minutes in a solution of gentian violet in aniline-water followed by alcohol for half a minute.

Friedländer[4] later stated that he had cultivated the coccus in blood-serum and gelatinized meat infusion and on potato. Introduced

[1] *Arch. f. Exp. Path.*, iv.
[2] *Mitth. a. d. k. Gesundh.*, 1881.
[3] *Virch. Arch.*, vol. lxxxvii.
[4] *Fortschritte d. Med.*, translated in *Micro-parasites in Disease*, New Syd. Soc.

by needle-puncture into the two former substrata, the growth takes the very characteristic form of a round-headed nail; on the latter ground it forms grayish drops. Diffused in distilled water and injected into the lung and pleura of rabbits, they produced no effects: but thirty-two mice died without exception, and generally in eighteen to twenty hours. The lungs were very red and almost universally solid, and the spleen was enlarged; both organs contained the characteristic cocci, which were present in considerable numbers in the blood and in enormous numbers in fluid which occupied the pleura. Guinea-pigs were more refractory to the poison, and only one dog of five suffered.

Inhalation-experiments were made by spraying water charged with cocci for five minutes into the cages of mice: three of ten developed pneumonia. The effect of chill was not excluded.

Baumgarten[1] is strongly of opinion that this parasite has no pneumonia-exciting action in man, but that it enters the pneumonic patch from the upper air-tubes or pharynx and multiplies in the inflamed tissue. For it seems that apparently identical "capsule cocci" are not uncommonly to be met with in pus, the epithelium of the mouth, sputum, or the secretion in nasal catarrh in otherwise healthy men: even the bacillus of rhinoscleroma is only with difficulty distinguished from these and from Friedländer's organism. Morphologically and in cultures the two latter are very similar, and their effects upon similar animals differ only in degree. Too much stress must not be laid upon even such close resemblance as this. A more serious objection lies in the fact that observers so highly qualified for the work as Weichselbaum have not been able to demonstrate this organism with the constancy of which Friedländer spoke, and, as the only organism present, it exists, according to Weichselbaum, in only 5.5 per cent. of the cases. For these Weichselbaum would retain it as the cause; but Baumgarten very rightly argues that a disease of such specific character as pneumonia is likely to be due to a single equally specific parasite (not, like suppuration, to several), and he believes that in Weichselbaum's method the truly specific organisms might have been missed or have died out. The strongest objection, however, seems to be that Friedländer regarded his coccus as retaining the aniline stain when treated with Gram's iodine solution, whereas the coccus which he cultivated is decolorized by this treatment, and the coccus which remained stained in sections of pneumonic lung prepared according to

[1] *Th.* 2, p. 244.

Gram's method were not the cocci Friedländer cultivated, but were those subsequently demonstrated by A. Fränkel and Weichselbaum, to the description of which we now pass.

A. Fränkel—and later, but independently, Weichselbaum—demonstrated the presence in pneumonic lungs of another organism—**pneumonia-coccus** or **Diplococcus pneumoniæ.** This consists in cultures of round or oval cells, usually in pairs, but often in chains of four to ten, or even twenty to thirty. These longer chains are much straighter than those of ordinary streptococci (Weichselbaum). In the tissues the microbes often become lancet-shaped, and their pointed ends may be toward or away from each other, usually the latter. These cocci have capsules just like Friedländer's, and their demonstration must be similarly effected. *They retain the aniline stain when treated by Gram's method.* Whereas Friedländer's coccus can be readily cultivated on gelatin, Fränkel's is best grown on agar at a temperature which would liquefy gelatin; the growth is scanty and not nail-shaped. The substratum must be kept slightly alkaline or growth ceases. Unless transferred daily from tube to tube, their virulence diminishes and soon disappears: to preserve it an occasional inoculation upon an animal must be had resort to. Cultivation for one to two days at 42° C. destroys their virulence; it is weakened by longer culture at slightly lower temperatures.

Subcutaneous injections of virus of full intensity into rabbits, mice, and guinea-pigs causes an acute, generally fatal, illness like septicæmia, with characteristic post-mortem appearances: there is no sign of pneumonia. But an attenuated culture introduced beneath the skin does sometimes give rise to pleurisy or pneumonia, or both, and these results are usual after injection of such a culture into the lungs. Then the appearances usually very closely resemble those in pneumonia and pleurisy in man, and the exudation contains large numbers of capsule-cocci. Pericarditis also may ensue.

An attack gives **immunity**, and the animal is most likely to survive the illness caused by simple cutaneous inoculation with the fresh virus. Inoculation with three- to four-day-old virus, repeated at intervals of a week, has a similar effect.

Baumgarten believes that this coccus may be regarded as *constantly* present, for, though Weichselbaum found it in only 92 per cent. of a large number of cases, his method of examination did not render it impossible to miss this coccus; and if it truly was absent in any cases, it was most probably dead at the time the cases were examined, for,

as in cultures, so probably in the body, the Diplococcus pneumoniæ has but a short life. These cocci occur in sufficient numbers to account for the symptoms.

Besides being found in pneumonic lung, it has been naturally enough found in the blood (sparingly) and in inflammations arising during the course of pneumonia—pleurisy, empyema, meningitis, endocarditic vegetations; in the more or less widespread œdema of connective tissue, which Weichselbaum has drawn attention to in pneumonia; and in the swollen spleen. But it appears to be an *occasional* denizen of the mouth, also occurring in the saliva of healthy people. This suggests that it is only an accidental parasite in pneumonia. Against this view the following points seem to tell: its inconstancy in the mouth; its constant occurrence in pneumonic lung, often as the *sole demonstrable organism;* its distribution, not uniform in the inflamed area, but chiefly at the spreading edge and in the surrounding œdema (Weichselbaum). The probability of its being the cause of pneumonia would, of course, be enormously strengthened if we could say that when introduced into certain animals it invariably induced this disease, but so far this has not been the case. Sometimes death occurs before there has been time for localization in the lung. Salvioli says that he succeeded in inducing lobar pneumonia in guinea-pigs by intratracheal injection of pneumonic exudation containing these cocci, but Fatichi failed with rabbits. Further experiments of this kind are required, for there is every reason to believe that in man infection occurs through the lung. This is the case, as it at present stands, for Fränkel's pneumococcus.

Other organisms have been described as the causes of pneumonia, but their claims are not such as to justify a description of them. We may just mention that when pneumonia runs on to suppuration and gangrene, these complications seem to be due to a secondary infection by the Staphylococcus pyogenes aureus or Streptococcus pyogenes.

Measles.—This disease has been given by inoculation of the healthy with the blood of the sick. Organisms have been found in the breath, in the blood, and in the skin, lungs, and liver. They are large, highly refracting, round or fusiform bodies, which remain unstained by carmine.[1]

Keating[2] says that he examined two series, each of eight cases, and

[1] Braidwood and Vacher, *Brit. Med. Journ.*, vol. i. p. 77, 1882.

[2] *Phil. Med. Times*, xii. No. 384, 1882.

found a special coccus constantly present in the papules; it was demonstrable in the blood in severe cases only. Here it either occupied the interior of leucocytes or performed swirling movements round them. The prognosis is bad if cocci are seen in the blood.

Cornil and Babes[1] found numerous diplococci in the interstitial tissue and vessels of the affected parts of the lungs of children dying with broncho-pneumonia. From the blood taken from papules a streptococcus was cultivated, many of the links of which resembled the diplococci above mentioned. Inoculated upon the skin of guinea-pigs, they caused redness of skin, conjunctivitis, and fever.

Vaccinia.—Chauveau and Burdon Sanderson showed by subsidence, filtration, and diffusion experiments that the virus of vaccine was particulate. Godlee and many continental workers have cultivated cocci from the fluid, some of the cultivations failing to induce vaccinia, whilst others succeeded. But the cause of their success seems to have been, not the cultivated cocci, but the vaccine virus, which they had neither discovered nor succeeded in eliminating. Koch and Feiler failed to cultivate from vaccine-lymph any germ capable of causing vaccinia.

Opinions still differ as to whether cowpox is, or is not, the result of inoculation upon the cow of the smallpox poison.

Cerebro-spinal Meningitis (epidemic).—Marchiafava and Celli found cocci constantly in the exudation, generally as diplococci: probably smaller than gonorrhœal organisms. They are not present in the organs generally, but are found in groups in the pia mater.

Micrococci have been described also in **Typhus**[2] (actively-moving, dumbbell cocci in blood in all [twelve] cases, and plugs of them probably in lymphatics in each of six hearts examined), **Variola, Acute Yellow Atrophy** of the liver (early stage), **Whooping Cough, Dysentery,** and many other diseases, but the evidence in favor of their causal relationship to the respective diseases is not sufficient to justify a description of them here. We may end the account of the pathogenic cocci by noting—on account of its historical and economic importance—that Pasteur very early proved that a fatal disease of silkworms, **pebrine,** is due to the action of a micrococcus (M. bombycis). The disease is hereditary, and the coccus is found *in* the eggs.

II. **Genus Sarcina** (Goodsir).—A micrococcus which divides in three diameters at right angles to each other is often found in vomit

[1] *Les Bactéries*, p. 621, 2d ed.

[2] F. W. Mott, *Brit. Med. Journ.*, vol. ii., 1883, p. 1059.

from stomachs dilated from pyloric obstruction, in cases of dyspepsia from chronic catarrh (Sarcina ventriculi), in the bronchi and deeper parts of the lungs in chronic inflammatory diseases, and in the urine (S. urinæ); it has been seen also in abscesses and in blood. Single cocci may be seen, but the majority form cubical groups of four or some multiple of four (Fig 167, $_4$). S. ventriculi is larger than S. urinæ or than the fungus of this shape occurring in the lungs. The presence of sarcina in the stomach does not cause it to appear in the urine or elsewhere. It is extremely difficult to get rid of the fungus when once established. The nature of the decomposition to which it gives rise is unknown. All attempts to cultivate it have failed.

Order 2.—**MICROBACTERIA**—one genus, **Bacterium** (the name "bacteria" has unfortunately been applied to the whole class). An endeavor was made to limit this name to cylindrical or oval cells of which the length was not more than twice the breadth, but as all rod forms vary in length the distinction is unimportant. These shorter rods are said to multiply by transverse division, are frequently seen in pairs and in zooglœa-masses, with much intercellular substance, but never in long chains. In cross-section the zooglœa-masses look like coccus-colonies, but rods may be seen at the edge. Spores have not been demonstrated. These fungi may be actively mobile or motionless.

Pigment-forming.—B. synxanthum occurs in yellow milk, the coloring-matter being soluble in water; B. æruginosum in greenish-blue pus.

Fermentative.—B. termo (Fig. 167, $_5$) is the most important species, being apparently a cause of putrefaction (Cohn). It is cylindrical, with rounded ends, 1–2μ long, often in pairs, and has a trembling movement. It is non-pathogenic, being unable to exist in living tissues; part of its action is due to the formation of unorganized ferments.

B. lineola, like, but much larger than, B. termo, often occurring with it, but also in fluids free from putrefaction.

B. lactis, the cause of lactic fermentation of milk (Lister).

Pathogenic.—A motionless bacterium of small size, lightly constricted in the centre, has been shown by Pasteur to be the cause of the disease known as "chicken cholera," though no symptom suggests a resemblance to cholera. That Pasteur early succeeded in attenuating the virulence of this organism and in conferring immunity from

chicken cholera by vaccinating fowl with the attenuated virus has already (p. 486) been mentioned.

Order 3.—**DESMOBACTERIA.**—Rods of which the length is more than twice the breadth, and generally considerably more, so that these fungi are slender. They multiply by transverse division, and often grow into long, jointed, but unbranched filaments, not constricted at the joints. Formation of spores has been detected in some species. Swarms of bacilli are common, but they are rarely imbedded in zooglœa. There are two genera—**Bacillus**, rods straight; **Vibrio**, rods curved.

Pigment-forming.—B. syncyanum occurs in blue milk.

Fermentative.—B. subtilis, found in hay-infusions and many other organic substances. Very delicate, actively moving rods, having a cilium attached at each end. When nourishment fails they become motionless, and bright oval spores form in their interior. It is an aërobious fungus.

B. butyricus, the cause of butyric fermentation. Rods vary from 3–10μ in length; slender at first, they become plumper, and the shorter ones appear spindle-shaped; oval spores form in their interior. The rods may grow into long or short chains, and in the latter condition quite lose mobility. Oxygen kills the bacillus (Pasteur).

Pathogenic.—The **Bacilli of Tubercle, Leprosy, Syphilis, Glanders**, and **Rhinoscleroma** are described in the sections devoted to these subjects.

Splenic Fever.—The B. anthracis, found in this disease, is the best known of all the parasitic fungi. Its life-history was worked out by Koch.[1] In blood from the spleen of animals dead of splenic fever are found enormous numbers of rods, 5–20μ long by about 1μ broad, straight, with slightly concave ends, and motionless (Fig. 167, $_6$). In a suitable culture-material (the blood of the dead animal is one), with a plentiful supply of oxygen and a temperature between 15° and 42° C. (25°–30° being most favorable), the rods grow into very long filaments (Fig. 167, $_7$); in these, round, highly-refracting spores form at short and regular distances; the filaments now break up and the spores are set free. Under favorable circumstances these grow into bacilli. In living animals long filaments and spores are never found, the rods multiplying solely by division. The rods exist in enormous

[1] Cohn's *Beiträge z. Biologie d. Pflanzen*, vol. ii., and *Mitth. a. d. Kaiserl. Gesundheitsamte*, vol. i.

numbers in the capillaries, especially those of the spleen, lungs, liver, kidneys, and mucous membrane of the intestine. Numbers leave the body in the urine, feces, and blood flowing from the nose and mouth of the animal before it dies; thus, the grass is covered with the fungi. In bodies buried at a depth of one meter oxygen and a suitable temperature are wanting, so no development of spores occurs and the bacilli soon die. Pasteur's belief that spores do develop under these circumstances and are brought to the surface by earth-worms is erroneous (Koch). As to the mode of infection: Pasteur says that the mouths of animals are wounded by siliceous grasses, and the cuts inoculated with bacilli or spores—a view supported by the frequent swelling of the cervical glands in sheep, but these animals and man are frequently infected by insects which bite them on the face. Koch thinks the intestine is the commonest seat of infection: Klein, however, records a case in which one mouse ate most of another, which had died of splenic fever, without ill results. In warm, marshy districts the bacilli form spores plentifully; these are carried by floods to meadows where anthrax may not have occurred previously.

In man, malignant pustule is due to inoculation with B. anthracis—in England generally from wool or hides brought from countries where the disease is endemic. Some time after the appearance of the pustule, as a rule, general symptoms appear, bronchitis or diarrhœa being common. Davies-Colley[1] found numerous bacilli in serum pressed from an excised pustule and in the sputum, urine, feces, and sweat. The patient recovered, but, though free from symptoms, he was still eliminating in his urine a few bacilli a month after excision of the pustule. In some cases there is no superficial lesion, and the symptoms may be those of acute septic poisoning or chiefly pulmonary or intestinal (woolsorters' disease). Perhaps the predominant symptoms indicate through which mucous membrane infection took place.

B. anthracis is constantly present in splenic fever, and ultimately in enormous numbers. Blood of the fœtus of an animal with splenic fever, which contains no organisms, does not produce the disease, whilst blood containing bacilli capable of development or spores always does in suitable animals. The bacilli may be separated by filtration and washed with distilled water, alcohol, ether, and then dried: they still cause splenic fever. Pure cultivations may be made through fifty generations with the same result. It never gives rise to any other disease. If this is not proof that B. anthracis is the *cause*

[1] *Path. Soc. Trans.*, 1883, p. 291.

of splenic fever, the belief that itch is due to the Acarus scabiei or that trichinosis is due to trichinæ must also be regarded as ill-founded.

Malaria.—This is regarded as the type of miasmatic diseases. It is endemic in low-lying places with undrained subsoil—swamps, marshes, and jungles: the alternation between the day and night temperature is often very great. The disease never becomes epidemic, and does not spread from man to man either directly or indirectly.

Marchiafava and Celli have endeavored to show that intravenous injection of malarious blood gives ague to men who have not previously suffered; but the experiment was performed in a malarious district.

The attacks are febrile and recur in early cases with great accuracy as to time every day (**quotidian**) or every other day (**tertian**), the between-times being afebrile and the patient well: in older cases it may skip two days (**quartan**) and the febrile attacks become atypical. Acute atypical forms (**perniciosa** and **typho-malaria**) and others in which the rhythm is more complex are known. Once affected, a patient may, after a long period of health, have another attack without any fresh exposure in a malarious district, and other maladies from which he may suffer subsequent to the attack of malaria are apt to assume more or less of a periodic type.

The cause of the disease apparently exists only close to the ground of the district, for the disease disappears at a quite moderate altitude, insufficient to affect the extreme alternations of temperature which some have regarded as the cause of the malady. The cause does not seem to be carried by the wind to any distance, nor by water.

Klebs and Tommasi Crudeli[1] examined the soil, water, and ground-air of malarial districts near Rome. They found in the soil very numerous mobile, long-oval spores ($.95\mu$ in greatest diameter), which on cultivation or on injection into an animal's blood grow into threads, $60–84\mu$ long by $.6\mu$ wide, homogeneous at first, but later dividing transversely. Spores form in the sections, at first parietal, afterward filling the whole interior (Fig. 167, $_9$). They are aërobious, and grow in albumen and fluids of the body, but not in water. Stagnant water of the district did not contain them. The air did, except during the seasons when malaria was not prevalent; then they were found in the soil only.

Culture-fluid, the filtrates of which had but slight effect, excited in

[1] *Arch. f. Exp. Path.*, p. 122, vol. xi.

rabbits typical, regularly intermittent fever, with swelling of the spleen, and in severe cases deposit of black pigment in it and in the liver. Developmental forms of the bacilli were found in the spleen, marrow, lymph, and blood.

The culture-method employed by Klebs being imperfect, it was said that he really worked with a mixture of germs. Schiavuzzi, therefore, obtained on a solid soil from malarious air a pure culture of the bacillus, and confirmed Klebs' results.

Marchiafava[1] a little later found the same spore-bearing bacilli in the spleen, marrow, blood, and lymph of patients dead of "perniciosa," and showed that they were frequently, but not invariably, present in the blood of patients during the *cold* stage of a fit; in the *hot* stage no bacilli were present, but the spores above mentioned were there in large numbers. Quinine caused the disappearance of these bodies. No organisms were present in the remission stage. Injection of blood into the trachea and peritoneum of dogs failed to produce the disease.

In the blood of a traveller recently returned from Africa Dr. McMunn found typical B. malariæ during the cold stage.[2] This seemed a strong point in favor of the etiological relation between this bacillus and malaria. But of the many who have since studied the disease, very few have succeeded in detecting the organisms of which Marchiafava gave such a specific account. Sternberg[3] failed to isolate it, and expressed the belief that Klebs had induced in rabbits a septicæmia, not an intermittent fever. Elaborate attempts to obtain cultures from the blood have been made, especially by v. Sehlen and by Marchiafava and Celli, without success, whereas Klebs' bacillus grows easily on ordinary media.

As the cause of malaria this bacillus has therefore given place to the **Plasmodium malariæ** or **Hæmatomonas malariæ**, a polymorphic, flagellate protozoon (as is believed) discovered and almost completely described by Laveran, working in Algiers;[4] found by Marchiafava and Celli in patients in Rome,[5] by Councilman in America, and by many others. A good account of the parasite from original observations is given by Osler.[6]

[1] *Arch. f. Exp. Path.*, xiii. [2] *Brit. Med. Journ.*, 1881, vol. ii. p. 935.
[3] *Nat. Board of Health Bull.*, Washington, 1881.
[4] *Traité des Fièvres palustres*, 1884.
[5] *Fortschritte d. Med.*, Nos. 14 and 24, 1885.
[6] *Brit. Med. Journ.*, 1887, vol. i. p. 556.

To see the hæmatomonas, take a drop of blood from a clean dry finger and get a *thin* layer between a cover-glass and a slide: a one-twelfth oil-immersion should be used. The following are believed to be its principal forms, and they are divided into *those occurring* within and *those external* to the red corpuscles: Certain—sometimes many, again very few—red corpuscles will be seen to contain a few or many dark grains (pigment) within a finely granular or hyaline body (the parasite). The red corpuscles so affected are usually larger, look flat, and are often pale. Only one amœboid body, as a rule, is present in each corpuscle. But there may be four. One may occupy only a fourth or practically the whole corpuscle. The pigment-grains frequently present Brownian movements: they alter their position with regard to each other, owing to changes in the protoplasm in which they lie; this performs slow amœboid movements. These bodies stain well with fuchsine or gentian violet.

Less often actively amœboid bodies containing no pigment-grains are found in normal or almost normal red corpuscles: they are probably an early stage of the form last described.

Occasionally solid bodies, from the size of a coccus up to a sixth of a red corpuscle, were seen apparently in a vacuole of varying form. In one case they were for days very numerous and the only abnormality. They stained deeply with aniline, and were sometimes themselves of a red-brown color.

Free in the blood were commonly found clear crescentic bodies with rounded ends, about twice as long as the diameter of a red corpuscle, motionless, containing a collection of pigment-granules about their centres. Changes in form are exceptionally seen. They are but rarely seen within either red or white corpuscles. One or two only may be found in a slide or six to eight in every field.

Next and more rarely may be seen round, finely granular, protoplasmic bodies, rather than red corpuscles, containing a central rosette of pigment. These may be contained in the membrane of a red corpuscle. Their protoplasm may be seen to become segmented, and in less than two hours to form a number of small spherical bodies, each with a central speck.

About as commonly flagellate organisms are found—usually one or two in a slide. They may be as large as a red corpuscle or half that size. They are round, oval, or pear-shaped, finely granular, and always contain pigment-granules. One to four very active flagella are present. Free flagella are sometimes seen.

Lastly, small, free, sometimes amœboid, pigmented bodies are common in some cases: the smaller are about the size of the products of the segmentation above mentioned.

All the forms described as occurring especially in red corpuscles are associated chiefly with *acute* forms, the crescents with *chronic* cases. The segmenting form occurred less often than once in ten cases, and always with the intracellular amœboid form. The flagellate organisms occurred in seven of seventy cases, in six chronic and one acute. The small, free, pigmented bodies seemed more abundant in chronic forms.

Osler could not satisfy himself that these forms of the parasite had very definite relation to the paroxysm. But Golgi states that in the intervals the pigmented bodies increase and fill the corpuscle, and finally the pigment collects in the centre. Fission coincides with the onset and course of the paroxysm, and the "rosette" forms disappear at its conclusion. Osler is disposed to support this.

Quinine invariably caused the intracellular pigmented bodies to disappear. After a few days in acute cases the corpuscles were free. Often crescents appeared before the blood became normal. Arsenic does not seem to influence the pigmented intracellular bodies. The crescent in chronic cases may last long, the health improving steadily, however.

As to the *constancy* of the organism, Osler missed it in eight out of seventy cases. In each of these he thinks the failure accounted for by insufficient opportunity for observation, previous exhibition of quinine, etc. He expresses no opinion as to whether the numbers of the parasite, when present, are sufficient to account for the symptoms.

The nature of the parasite is discussed by Crookshank.[1] He considers it to be identical with a hæmatozoon of the carp and mud-fish, with Lewis' hæmatozoon of rats, and with a parasite found by Surgeon Griffith Evans in the blood of horses, camels, and mules suffering from a fatal febrile, periodic disease called *surrah*. It is believed that this parasite destroys the red corpuscles and consumes the pigment.

The exact order in which the forms above described succeed one another in development is unknown. The amœboid forms have not been seen either to enter or to leave a red corpuscle, nor has a crescent been seen to leave, though it is apparently formed within a corpuscle.

The leucocytes may be in excess, commonly contain pigment-granules, occasionally forms of the parasite.

[1] *Journ. of Roy. Micros. Soc.*, 1886.

Typhoid.—Klebs first described micro-organisms in this disease.[1] He and his assistants found them without exception in twenty-four cases of typhoid—constantly in the bowel and frequently in mesenteric glands, kidneys, spleen, heart, laryngeal cartilages, in patches of lobular pneumonia, and in the pia mater (one case with severe cerebral symptoms). The organism was a short rod which grew into long, narrow, unbranched filaments, of which the diameter increased as spore-formation took place. Klebs cultivated the organism on gelatin, but it is uncertain whether his cultures were pure. He also inoculated rabbits from the cultures, and in one case some swelling of Peyer's patches was found post-mortem.

A few months later Eberth[2] described bacilli with rounded ends as existing in the intestinal lesions, mesenteric glands, and spleen. He said that they stained badly with aniline dyes, and worked with unstained specimens clarified by an alkali. He was thus able to discover the bacilli in eighteen out of forty cases. He believed them to be the same as Klebs described, but regarded the filaments, of which the latter author spoke, as secondary. Eberth stated that the number of bacilli diminished with the duration of the case.

Koch[3] had already photographed similar bacilli at the time Eberth published. He found that they stained well with Bismarck brown, and had demonstrated their presence in half the cases examined by him.

W. Meyer[4] took for examination only recently-swollen patches and follicles. He failed to stain the bacilli, but found them in sixteen out of twenty cases.

All the above observers made control-observations on other cases, such as tubercular ulceration of the intestine, but they never found the typhoid bacillus in diseases other than typhoid. They sometimes found cocci in the intestine and glands, and regarded them as secondary; but by others, as Leitzerich,[5] they have been considered as the organism of the disease.

Coats and Crooke[6] each found the bacilli of Eberth and Koch in mesenteric glands.

A very important paper by Gaffky, one of Koch's assistants, next

[1] *Arch. f. Exp. Path.*, vol. xii. p. 231.
[2] *Virch. Arch.*, vol. lxxx. p. 58, and vol. lxxxiii. p. 486.
[3] *Mitth. a. d. k. Gesundheitsamte*, vol. i., 1881.
[4] *Unters. ü. d. Bacilli d. Abdominaltyphus*, Inaug. Diss., Berlin, 1881.
[5] *Arch. f. Exp. Path.*, vol. ix. [6] *Brit. Med. Journ.*, 1882, March 18 and July 1.

appeared.[1] He starts with the observation that the bacilli have been found in only half the cases examined. They must therefore have either disappeared before the disease which they caused had run its course, or they were present, but not found. The latter seemed probable, as they had been demonstrated late in some cases and missed at early stages in others. He points out that in typhoid the bacilli are not scattered everywhere, but are always in foci, and therefore more difficult to find, and that but little of an organ has been examined, even after one hundred sections have been carefully looked through.

Gaffky himself investigated twenty-eight cases, and in twenty-six demonstrated the presence of bacilli in parts other than the intestine, such as the mesenteric glands, spleen, liver, kidney. In the other two cases the bacilli were found in a recently-swollen solitary follicle of one, and the other died at the end of the fourth week of perforative peritonitis, and the intestines showed only healing ulcers.

In one case, which Gaffky does not include in his list, although it had been diagnosed as typhoid both during life and post-mortem, immense numbers of cocci were found in the organs, and it was impossible to distinguish the typhoid bacilli. Gaffky throws out the suggestion that there may be a disease clinically like typhoid due to invasion of the intestine by cocci.

The bacilli were more numerous the earlier the case. If many are found in old cases, it is probable that a relapse has occurred.

The process employed to demonstrate the bacilli was to harden pieces of *fresh* organs in alcohol, and to place sections cut from them in methylene blue for twenty-four hours. The solution is made by adding a saturated alcoholic solution of the blue to water until the latter cannot be seen through. The sections are clarified and mounted in the ordinary way. Blue sections lose their color rather quickly; those stained with Bismarck brown are better for preservation. It is most important that the organs should be fresh, for the bacilli are difficult to distinguish in sections from putrefactive organisms.

The bacilli are thus described (Fig. 167, $_5$): They are three times as long as broad, and their length equals one-third the diameter of a red blood-corpuscle. Their ends are distinctly rounded. Spores are not uncommonly seen—round, reaching right across the breadth of the rods, and lying at their ends. The typhoid bacilli are more or less actively mobile. They do not stain so intensely as other forms, and sometimes they do not stain uniformly; round spots not extending

[1] *Mitth. a. d. k. Gesundheitsamte*, vol. ii. p. 372, 1884.

across the rods, and therefore not spores, being left pale. The typhoid bacilli do not stain like tubercle-bacilli (p. 526).

Thirteen cultures were made from spleens, and eleven were pure from the first; peptonized meat-broth stiffened with gelatin was the soil used. It was spread in thin layers upon slides, and these were inoculated in streaks and kept moist under a glass bell. In twenty-four hours increasing cloudiness could be seen confined to the lines and *not causing liquefaction* of the soil: it was due to roundish, slightly granular, yellow-brown colonies. A little mixed with sterilized water examined with a one-twelfth oil-immersion showed the colonies to consist of one form of bacillus only, like, but rather larger than, that in the spleen whence culture was started. They were three to four times as long as wide; apparently the soil suited them better, so they grew more strongly, as they did also on potatoes; whilst in blood-serum they remained of the same size as in the body. Spores form at the ends of the rods in three to four days at 30°–42° C., more slowly at 20° C., and not at all below this point. In smaller number than the rods jointed threads also formed. The cultures reached their height in four to eight days, and then remained stationary. The mode of growth in both gelatin and potato was characteristic. Cultivation was continued on the gelatin in ten cases for more than a year without any change occurring in the organism.

In two cases putrefaction had begun in the spleens used, and other organisms, cocci and bacilli, liquefying the gelatin, also grew; but in this solid culture-ground it was so easy to select typhoid bacillus-colonies that the second culture was quite pure.

In one case in which a culture from the spleen succeeded no bacilli were found in cover-glass specimens nor in sections until over one hundred had been examined. The method of culture would seem to be the most delicate for the detection of the organisms.

A culture from the liver was tried in one case and succeeded.

Many animals of different kinds were inoculated, but unsuccessfully. It is very doubtful if any animal suffers from the typhoid fever of man. In spite of this gap in the chain of evidence, all the observers quoted believe that this bacillus is the cause of typhoid; and we may now say it is constantly present in typhoid, is recognizable from all known bacilli by the various characteristics given above, and is not found in any other disease. Gaffky believes that infection occurs always through the mucous membrane of the intestine; even when the poison seems to have been inhaled as dust, he thinks it sticks on the

pharynx, is swallowed, passes through the stomach, and thus reaches the bowel.

At the International Medical Congress in 1881, Bouchard stated that he had found bacilli in the tubules and in intertubular tissue in cases of tubal nephritis occurring during typhoid. They have been described by other observers as occurring in the urine.

Septicæmia of Mice.—Koch[1] injected putrid fluids subcutaneously in mice in quantity too small to cause septic intoxication. A peculiar disease, without abscess-formation, occurred in some individuals, and was transmissible with certainty to others by inoculation of a very small quantity of blood. Extremely small bacilli, chiefly in leucocytes, were shown to be the cause of the disease. One attack confers immunity. It is not inoculable upon field-mice or rabbits.

Malignant Œdema.—A spreading œdema ending fatally may be produced by inoculation of mice, guinea-pigs, or rabbits with garden mould. One form of fungus develops, and the œdema-fluid containing it is easily inoculable.

There are two species of the genus **Vibrio**, V. rugula and V. serpens; they occur in putrefying fluids and are not pathogenic.

Order 4.—**SPIROBACTERIA.**—These differ from Vibrio in making more screw-like and closer turns; river-water is their favorite habitat (Cohn). There are two genera—Spirochæta, flexible, with wide thread; Spirillum, stiff, with narrow thread.

Relapsing Fever.—The Spirochæta Obermeieri (Fig. 167, $_{10}$) often called spirillum, is found in the blood in this disease. It was discovered by Obermeier in 1873. It is 16–40μ long, and makes quick undulating movements. The organisms are generally said to appear in the blood soon after the commencement of an attack, and to disappear with remarkable speed after the crisis. Spitz, however, states[2] that by careful examination he found spirochætæ in the blood two to four hours before and after an attack. Nothing is seen of them till the relapse, when they return. The disease has been inoculated from man on man and from man on apes (Carter, Koch). Cultivation has hitherto not succeeded.

It is said that blood taken in the fever-free period is not infective; no spores are known, and the spirochæta has not been found on the tissues. We give the following experiments as bearing on the point,

[1] *Traum. Infect. Dis.*, p. 33.

[2] *Diss.*, Breslau, 1879.

but they certainly require confirmation: Albrecht[1] took blood from patients after an attack of recurrent fever, kept it in a moist chamber, and examined it frequently. In the first day of the remission he found (1000 diameters) extremely small movable bodies; later these were succeeded by slender rods, each bearing a spore at one end or in the middle; and finally, active spirochætæ appeared after the relapse had begun in the patient from whom the blood was taken.

A spirochæta is often found in carious teeth.

The **Spirilla**—tenue, undula, and volutans—are not pathogenic.

Cholera Spirillum.—The infective nature of cholera has long been maintained by many observers, and several announcements of the discovery of the parasitic cause have been made. With one or two exceptions, however, the parasites have proved to be the spores of common moulds or some simple and widespread fungus. No certainty had been arrived at up to 1883, when Robert Koch went to Egypt as chief of a commission sent by the German Government to investigate the matter. The commission subsequently went to India, and there completed their examination of cases.

Koch was first struck by the discrepancy between the accounts in text-books of the **post-mortem appearances** of the diseases and what he actually found. Shortly, he observed that it was quite rare to find the intestinal mucosa simply opaque with slightly swollen follicles and the intestinal contents like gruel: this happened only in the most acute cases, and the gruel-like contents presented almost a pure cultivation of the parasite presently to be described. Koch only very exceptionally found in the intestines any fluid so thin as to be comparable with rice-water. In cases of somewhat longer duration he found the follicles and Peyer's patches surrounded by zones of hyperæmia, soon running together into red patches; and ultimately in the longest cases the small intestine became intensely congested, the congestion being most marked above the ileo-cæcal valve and dying away in the upward direction. With these changes the intestinal contents became increasingly bloody, and finally exhaled a distinctly putrefactive odor, whilst the parasite above referred to was more or less replaced by other bacterial forms.

In the stage of patchy redness sections of the mucosa parallel to its surface showed that the redness corresponded to an invasion of the epithelium of the tubular glands by the parasite found in the intestine

[1] *Petersbürg. med. Wochschr.*, 1880, No. 1.

in the most acute cases: they were found lying between the epithelium and the basement membrane. This bacterium, therefore, soon attracted attention by its definite form and by its apparent constancy.

Characteristics of the Cholera Spirillum.—The bacterium is about one-half to two-thirds the length of a tubercle bacillus, but decidedly thicker (about .5μ), and it presents a curve, usually about equal to that of a comma (hence the first name—comma bacillus), but sometimes amounting to a semicircle. It multiplies by transverse division, and the segments separate from each other at once upon gelatinous media or the intestinal mucosa; if two remain united they form an S, their curves being in opposite directions. When vegetating in good nutritive fluids, however, the segment-cells remain united until they form delicate spirals of some length, very like the spirillum of Obermeier; in fact, Koch says that side by side under the microscope he could not distinguish them. Each segment-cell forms about half a turn of a spiral form, and the width of the spiral is about equal to the thickness of a cell. Both single cells and spirals are actively mobile. It grows well upon all the ordinary media, and its rapid multiplication can be watched in a drop of meat-infusion upon the under surface of a cover-glass; also in stains of cholera dejecta upon linen, kept moist and exposed to the air, growth is very free for two or three days. The colonies upon nutrient gelatin or agar begin as very pale tiny spots, which, as they get larger, present a slightly irregular outline and a finely granular surface: Koch compares them to heaps of fine bits of glass. Then the gelatin (not agar) around for about one millimeter gets liquid, and the colony sinks into a funnel-shaped depression with an apical white point. The appearance of a long narrow funnel is very typical when a tube is inoculated by puncture.

The growth of this spirillum is unusually rapid: it reaches its limit in a few days, remains a short time stationary, and then diminishes, the bacilli either shrivelling or swelling up centrally or terminally, and staining more or less imperfectly. Many strange "involution-forms" appear, and have been thought to belong to different species. Clear spots failing to stain have often been taken for spores; but Koch early showed that spirilla containing these spots were obviously dying, for they failed to grow and did not possess the resisting power of spore-bearing organisms. He believed that no spores formed; but Hüppe has described the splitting up of vegetative cells

into small fragments, which become rounded like spores, and these when transplanted grow into spirilla (*arthrospores*).

Growth is most rapid at 30°–40° C., and stops below 16° C. Death is not caused by freezing at 10° C. for some hours, but it results certainly from a temperature of 55° C. Oxygen is most essential to growth, but neither its absence nor an atmosphere of CO_2 causes death. An alkaline reaction is most favorable, and distinct acidity often stops growth; but all acids do not do so, for the surface of a potato is acid, yet growth occurs freely upon it. Koch added many antiseptics to cultivations to discover those which most powerfully hindered development. Quinine (1 : 5000) and perchloride of mercury (1 : 100,000) head the list, but it is obvious that the constitution of the material to which they are added will greatly affect the result. Koch's most important observation of this kind was that complete **desiccation** kills the vegetating cells of these bacteria in three hours; it must be remembered that in pappy substances it may require many hours to desiccate completely, but even in such twenty-four hours suffice to destroy cholera-germs. On the other hand, Hüppe has obtained fresh cultures from arthrosporous spirilla after four weeks' desiccation, and vigorous growths have been obtained from desiccated cultures after ten months. It is not yet certain, but Hüppe believes, that arthrospores were contained in the latter, and that new growths after long intervals always arise from these structures. Lastly, it is very probable, if not certain, that this spirillum soon dies in putrid fluid, cesspools, and the like, and that consequently the addition of antiseptics to such collections of matter may possibly preserve rather than destroy the cholera-germ.

Koch was strongly of opinion when he wrote his early papers on this subject that the form of the "comma-bacillus" was quite characteristic; but Finkler and Prior discovered a spirillum very like it in "English cholera;" Deucke found another in cheese, and Lewis a third in the human mouth; Koch found a bacterium like it, but thicker, in the water of the Hooghly. Careful study of their plate and tube cultivations and of their pathogenic effects has shown that these very similar organisms are radically different. Lewis' spirillum has not yet been cultivated.

It would seem from the above morphological and physiological details that Koch's cholera-germ is a perfectly distinct organism. All that more recent observers have added to this account of it, which we have taken almost entirely from Koch's writings, is that the bacte-

rium does not seem constantly to invade the intestinal epithelium. Some have claimed to find it in cultivations from the blood and various organs, but there is much doubt as to the correctness of the observations, or at least as to their general applicability.

Koch's theory as to its action is that, being confined to the intestine, it produces a virulent general poison and at the same time irritates violently the mucous membrane. Early death in collapse, perhaps before the passage of a single stool, may occur from general poisoning, and it is in these cases that the intestine is found pale, simple hyperæmia having died away. In longer cases the local effects become more marked, and increasing extravasation of red corpuscles remains to mark the existence of the hyperæmia. Then the cholera-germ, having reached its limit of development, being perhaps hindered from further growth by the products of its own action, is more and more replaced by putrefactive germs, the products of which are both extremely irritant and poisonous. Some modification of this view would be necessary were it conclusively shown that the cholera-germ multiplied in the blood and various organs.

Koch found this spirillum in 10 Egyptian and 42 Indian cholera cases; in the stools of 32 cases; twice only in vomit, the intestinal contents (alkaline) having in these cases been brought up; in material of 8 cases sent from India, and in 2 at Toulon. Practically, all observers, even those having a germ of their own to run, have reported similar results, though some have found it scarce, the cases being probably of long duration. We may therefore take it that *Koch's cholera-germ is constant in the early stages of the disease.*

Next, Koch examined the intestinal contents and stools of a large number of cases—dysentery, intestinal catarrh, ulceration, typhoid and typhus, diarrhœa of adults and children; the stools of animals, normal and after arsenical poisoning; the contents of the Calcutta drains; and water from the most varied sources. Only once, in a tank in a cholera district, was the spirillum found external to the body, and here it seemed to have a clear relation to the epidemic around it. Koch therefore concludes that *this spirillum occurs only in cases of cholera;* its discovery, therefore, in diarrhœa-stools (most epidemics begin with cases of diarrhœa) would be most important.

Lastly, as to the **relation of the comma-spirillum to cholera** three views are possible:

1. The cholera process favors this spirillum, which therefore multiplies rapidly. But as it is constant in cases of cholera, it must, on

this view, be constant in the alimentary tract of healthy people: which is not the case.

2. During the cholera process the conditions may induce some ordinary bacterium to assume this form and development. There is no evidence of such change in this or any other bacterium.

3. *The spirillum is the cause of cholera*, and this Koch regards as proven. He at first failed entirely to produce anything like the disease in animals, and endeavored to support his views by cases of infection from man to man. Thus, both in India and Europe those who wash linen soiled with cholera dejecta have frequently become infected. The tank in which Koch found the spirillum had been infected by the washing in it of the clothes of the first case. The spirilla evidently multiplied rapidly, and the epidemic *followed* on this *pari passu*, dying away as the germ disappeared. Then the following is reported by Macnamara:[1] By an accident cholera dejecta became mixed with water which was drunk by seventeen persons; of these, five had cholera. Lastly, during a course of demonstrations at Berlin upon the bacteria of cholera one of the attending physicians was attacked by what seemed to be a distinct though mild form of the disease, his stools containing numbers of spirilla.

Meanwhile, Nicati and Rietsch at Marseilles succeeded in infecting dogs and guinea-pigs with a disease like cholera by injecting cultivations of the spirilla into the duodenum, and their results were repeated and confirmed by Koch and others. This method was adopted to avoid the stomach, in the acid secretion of which the cholera-germs ordinarily perished. Of eighteen guinea-pigs thus treated, thirteen died of "cholera;" whilst of control animals, injected with other bacteria, none died.

The method of infection being far from analogous to that which must prevail in man, Koch first examined the natural system of digestion in guinea-pigs by a beautifully adapted series of experiments. He found that substances passed rapidly through the stomach, and especially the small intestine, down to the large cæcum, where the contents again became acid, and that, unless in the form of spores, live germs failed to pass the gastric juice. He therefore neutralized this for about three hours by a suitable injection of carbonate of soda, and later injected spirilla in meat-infusion. Of nineteen animals, only one sickened and died with symptoms such as occurred after injections into the duodenum; this was an animal that had recently

[1] *Quain's Dict.*

aborted—an occurrence which, with the flaccid abdominal walls, suggested that possibly peristalsis had been delayed. This was therefore done experimentally by means of opium, and the result now came out that of thirty-five guinea-pigs infected by the stomach thirty died of "cholera."

Finkler's and other "comma" bacteria were similarly examined, and very distinct differences between them and the above organism were found.

Infection by the stomach would apparently be much easier in man than in guinea-pigs. Ewald finds that water introduced into an empty stomach remains neutral, or even becomes slightly alkaline; its quantity slowly decreases for one to one and a half hours, then suddenly does so before its reaction has become acid, evidently from opening of the pylorus. Cholera-bacilli introduced shortly before this juncture would surely reach the duodenum alive. Further, when Koch wrote this he was unaware that arthrospores formed. It would therefore seem possible that the cholera spirillum should occasionally pass through the stomach of man without predisposition. But, as with other acute specific diseases, of those exposed but few take the disease, and according to Koch almost all these had digestive troubles, gastro-intestinal catarrh or an overloaded stomach, the latter condition diminishing the general acidity of the stomach and enabling the spirillum to pass with undigested masses.

The *contagion* of cholera *exists in the dejecta*, and quite exceptionally in vomit (when this has regurgitated from the intestines). For *spread* to occur moisture is essential, as short desiccation as a rule (see above) means death: cholera, therefore, does not, like tubercle, spread by the shaking of dust from linen, etc.: it is not carried by post nor by merchandise, but by man. As a rule, it is spread by the infection of water: this occurs very easily in India, where a large tank is employed to collect water for many people, and is used by them as a public bath, wash-tub, cesspool, and for the supply of drinking-water. Koch quotes convincing examples to show that the supply of pure water will prevent the occurrence of the disease where previously it has been rife. Moist provisions may be infected by contaminated hands or perhaps by flies.

This parasite can certainly multiply external to the body—*e. g.* on moist linen, meat-infusion, potato. As it requires rather concentrated nourishment, it probably does not multiply in ordinary running water; but many of the rivers of India are extremely foul, and organic mat-

ter increases greatly where the waters stagnate, drains and gutters enter, and vegetable and animal refuse collects: round about such masses water may be muddy from germs. Stagnant surface-water, therefore, seems to be the great culture-ground for cholera-germs external to the body.

All evidence goes to show that *the home of the cholera-germ* is the delta of the Ganges—a region so peculiarly adapted to the growth of micro-organisms by the quantity of dead animal and vegetable matter, the heat and the moisture, that one might expect to meet with quite special forms of bacteria. To this region careful inquiry has always been able to trace epidemics of cholera. Of course there is no *a priori* reason why the cholera-germs should not be evolved under similar conditions elsewhere, but, so far as we know, this has never occurred.

We must end this account by stating that Emmerich has endeavored to establish a motionless bacillus, known as the *Naples bacillus* (from having been found in the organs of cases dying at Naples), as the cause of cholera. But the accounts which he and other observers give of it do not tally, whilst they all bear witness to the constancy of Koch's spirillum. To quote from De Bary: "From the material before us the unprejudiced critic cannot, in my judgment, find any valid objection to the views of Koch and his school."

The Blastomycetes or Yeasts.

These are small round or oval cells, which multiply by gemmation. Sometimes the cells cohere and form branching chains. When food is not abundant, as when cultivated in potato, turnip, etc., one to four spores may form in the interior of the yeast-cells; these develop when placed in fermentable fluids. Under the same conditions unjointed mycelium may be produced. These facts, taken with the knowledge that some higher fungi (*e. g.* Mucor mucedo) under certain circumstances grow as yeasts ordinarily do, by gemmation, make it possible that yeasts are really vegetative forms of higher fungi.

Yeasts are of importance only as causes of fermentation. They never invade living tissues. They are not rare in the stomach, either alone or in company with sarcina. They are frequently found in diabetic urine, but not when it is passed.

Thrush.—In this disease tolerably adherent gray or milky patches form in the mouth, pharynx, and gullet, either of children at the breast or of adults exhausted by disease (typhoid, phthisis). These

patches are due to the growth of the **Oïdium albicans**, a parasite which was regarded as a mould; but Grawitz states that when cultivated this fungus shows itself to be a yeast, and probably the Mycoderma vini, which he has proved capable of growing on mucous membranes. The patches consist of tortuous, often branched filaments, formed of long cells united end to end, and distinctly constricted where they join. The filaments end in roundish cells, which produce one or more spores; these form heaps in the epithelium.[1]

The Hyphomycetes or Moulds.

These consist of filaments (hyphæ) formed by a single row of cells placed end to end, growing by means of an apical cell which elongates and divides transversely. Lateral offshoots are common, but dichotomous branching is rare. The thallus may consist of a single hypha: usually the hyphæ are numerous and intercross loosely or closely. All spring from an axis or *germinal tube* which grows directly from a germinating spore. Compared with that of bacteria (p. 471), their growth is extremely slow.

In the adult plant the hyphæ are of two kinds—*nutritive*, which grow into and extract nourishment from the culture-soil, forming in it by their interlacement the *mycelium*; and the *reproductive*, which spring from the mycelium and stand up from the substance in which the mycelium lies. These are called fruit-hyphæ; they are simple or branched, and bear at their ends spores or sexual organs. Reproduction is either asexual or sexual; the two methods may occur together on the same plant or may alternate regularly or irregularly. Spores are formed by each—round, oval, or cylindrical, smooth or irregular, colored or colorless; most are motionless, but some "swarm." Each consists of a little mass of protoplasm surrounded by an envelope, which is made up of an outer (*exosporium*) and an inner (*endosporium*) layer; the exosporium is often pigmented. All spores have great power of resisting the action of physical and chemical agencies, and retain life for long periods; those formed asexually are ready at once to germinate, but those due to a sexual process almost always require a rest. The latter are the true *resting-spores*; but this name is often applied to all spores capable of retaining life for long periods in spite of adverse conditions.

To understand the above and what follows the student should

[1] *Virch. Arch.*, vol. lxx.

examine a few moulds from the surface of thin jam, paste, decaying fruit, or the surface of a slice of potato which has been exposed for an hour or two in a dwelling-room. In all the aërial portion is easily studied, and the mycelium is readily shown by crushing a bit of the culture-ground under a cover-glass.

Asexual spore-formation occurs in three ways:

1. Hyphæ spring from the mycelium and perhaps branch. The terminal cells divide transversely into spores (*conidia*), which either fall away singly or form chains.

2. A hypha (*sporangiophore*) stands up from the mycelium, and its end swells into a ball full of protoplasm, which segments and forms conidia (*sporangium*).

3. From the surface of a knob on the end of a hypha (*conidiophore*) peg-like processes (*sterigmata*) sprout; each sterigma, by growth and transverse division, forms a chain of spores.

Sexual reproduction occurs in three ways:

1. **Conjugation.**—The apical cells of two hyphæ meet end to end and blend into one cell (*zygospore*). From this, after a longer or shorter rest, a sporangiophore sprouts, and from its spores new plants grow. (Any of the Mucorini.)

2. **Fertilization.**—(*a*) The end of a hypha becomes twisted like a corkscrew, more and more closely, until its turns form a continuous tube—the *ascogonium*. From its lower turns spring fine branches, one of which (*antheridium*) conjugates by its apex with the ascogonium; the others simply cover the ascogonium continuously, and are converted by division into polygonal cells which form a capsule (*perithecium*) round it. Many transverse septa form in the tube of the ascogonium, and from the cells thus produced flask-shaped lateral projections (*asci*) develop; in each of these eight spores generally appear. The perithecium thins greatly as the asci enlarge, the walls of the asci disappear, and an easily-ruptured sphere of spores remains. When these germinate the endospore swells, splits the exospore, and puts out the germinal tube, whence springs the mycelium. This again gives origin first to conidiophores, then to perithecia. Eurotium repens and Aspergillus glaucus, found especially on preserved fruit, show these changes.[1]

(*b*) In some species certain cells form an organ (*oogonium*) in which female reproductive bodies (*oospheres*), one or more, are formed; whilst other cells form a male organ (*antheridium*) in which *spermatozoids*

[1] Sachs, *Text-Book of Botany*, p. 257.

are produced. The oosphere, which is hundreds of times larger than the spermatozoids, remains in the oogonium, and is there fertilized by the mobile spermatozoids. It is now called an *oospore*, and may, after a rest, develop directly into a new plant, or form cells, each of which does so.[1]

Conditions of Life—Food.—Possessed of no chlorophyll, moulds are unable to build up carbon-compounds: they assimilate those built up by other plants or animals. They are therefore always either saprophytes or parasites; in the latter case they may kill their host. They require a free supply of oxygen; but some can obtain it, at least for a time, by decomposition of organic compounds like sugar. Thus, Mucor racemosus, cultivated on the surface of a saccharine liquid, absorbs oxygen, oxidizes completely some of the sugar, exhales carbonic acid, and grows rapidly. If deprived of oxygen, as by immersion, only the mycelium grows, and this becomes broken up into short cells, which multiply by budding and much resemble yeast-cells. The growth is much slower, carbonic acid escapes in bubbles, and alcohol appears in the liquid. But soon all stops, and the process can be started again only by a fresh supply of oxygen.[2] Some moulds, as Penicillium glaucum, Aspergillus niger, have no power of thus obtaining oxygen, and die if cut off from the free gas. The change in the character of growth above mentioned, accompanying change in conditions of life, is often pointed to as evidence in favor of the mutability of bacteria.

Light.—Many moulds can develop completely without it: some require it for the discharge of spores and other processes.

Temperature.—Ziegler states that moulds flourish best at temperatures below that of the body (37.5° C.), and that some will not grow at this point. A few species of Aspergillus and Mucor grow well between 35° and 40° C. The spores are as resistant to external agencies as are those of bacteria.

Water is essential, but mere dampness is sufficient.

Action.—Moulds are associated with processes of *rotting* or *decay*. The peculiar smell and taste which they impart are known to all. The products of their life-action have not been closely investigated, but they are neither very poisonous nor irritant to man.

Distribution.—The spores of moulds are much more numerous in the air than are other organisms. They therefore constantly fall upon the skin and enter the air-passages with air and the food-passages with

[1] *Text-Book of Botany*, p. 212. [2] Duclaux, p. 54.

food. As a rule, they find no nidus suitable for their development; the supply of free oxygen is often insufficient and the temperature too high. Certain of them, however, when brought into contact with accumulated inflammatory discharges or with sloughs take root and fructify. This is most likely to occur in the respiratory tract and the alimentary tract above the gullet. They are here saprophytes, but the products to which they give rise may irritate the living tissues lying beneath the soil in which they grow. Species of Mucor and Aspergillus are those commonly found.

Pathogenic Moulds.—Owing to the peculiarities mentioned in their life-history, these fungi have but little power of invading living tissues. Certain skin diseases are, however, due to the growth of species of this class in epidermic structures: they are—favus; tinea tonsurans, kerion, circinata, sycosis, and unguium, and tinea versicolor. Two diseases, actinomycosis and the Madura foot of India, have been attributed to penetration of the deeper tissues by hyphomycetous fungi.

Favus.—The Achorion Schönleinii forms almost wholly the light, yellow, mouldy-smelling crusts characteristic of **favus**. When in hairy parts, which are the usual seats, the hairs are always invaded, especially the roots. Here the parasite grows luxuriantly, but it does not extend far up the shaft; its primary seat is the epithelium of the hair-follicle. On non-hairy parts the mycelium invades the deeper layers of the epidermis. The mycelium consists of unjointed, branching, confusedly-intercrossing tubes; in certain of them, which become divided into joints, oval spores form.

The nails are very rarely affected, and chiefly by mycelium.

The Trichophyton tonsurans is the cause of tinea tonsurans, tinea kerion, tinea circinata, tinea sycosis, and tinea unguium.

In **tinea tonsurans** the hair is chiefly affected; the root and the lower part of the shaft are crammed with spores which lie in rows between the fibrils of the hair. The weakened hair breaks beyond the scalp, leaving a stubby line of fracture. Epidermic scales from the surface may contain fungus, but the deeper living cells of the root-sheaths never (Thin and Taylor). Spores are abundant, and oval in shape; mycelial threads are rare. Points worth remembering in relation with the undoubted fungoid origin of the disease are its occurrence in children only (speaking broadly), the predisposition to it shown by some, its great contagiousness when acute, diminishing as it becomes chronic, and its more severe course when contracted from

animals, as the horse. It may excite severe irritation and even suppuration—T. kerion.

Tinea circinata.—Here the parasite infests epidermic cells, always causing desquamation, sometimes vesiculation or even more severe inflammation. Mycelium is chiefly present in the form of very long, jointed and branched threads; the spores are scanty, single, or in short chains. The fungus altogether is often scanty, and is especially difficult to detect if it has excited inflammation.

Tinea sycosis.—When attacking the beard the fungus is found chiefly in the hair, but also in the follicle; both mycelium and spores are seen, the latter in excess, but not so markedly as in T. tonsurans. The mycelium generally lies round the root of the hair, and is pulled out of the sheath with it. Severe inflammation is generally excited.

Tinea unguium.—Mycelial threads of trichophyton may occasionally invade a finger-nail, rendering it opaque, thick, and brittle. Unlike a general condition, the fungus produces these changes in one to three nails only, and the toe-nails are scarcely ever affected. In this situation it is extremely difficult to destroy.

Chloasma, Pityriasis versicolor.—Microsporon furfur invades the horny layer of the epidermis of covered parts of the trunk, growing more superficially than any of the above, rarely causing irritation and not attacking nails or hair. It consists of jointed mycelial threads, which are always abundant, and spores, which vary much in form and grow at the ends of the mycelial threads.

Actinomycosis.—The ray fungus (*actinomyces*) is believed to be the cause of this disease. It has been described at p. 354. Its botanical position is doubtful.

Madura Foot.—In certain parts of India the feet of natives only swell; tubercles form beneath the skin, burst, and leave sinuses from which bodies like those constituting the roe of a fish are discharged, or, more rarely, bodies like grains of gunpowder. In the former fungi have never been found; but in the latter, after soaking for some days in potash, fungous elements have been recognized, and called Chionyphe Carteri. These are believed by some (V. Carter) to be the cause of both classes of the disease. Cunningham and Lewis do not hold this view.[1] On section, masses of the above bodies are seen, especially in the fatty layer; the masses may have no obvious communication with each other or with the surface. The botanical position of the fungi found is doubtful.

[1] *Quain's Dictionary.*

METHODS OF DEMONSTRATING THE PRESENCE OF PATHOGENIC MICRO-ORGANISMS.

These vary according as they are used for the investigation of (*a*) fluids or (*b*) tissues.

(*a*) **MICRO-ORGANISMS IN FLUIDS.** — 1. Simple microscopic examination may be sufficient to reveal organisms of distinctive form or possessing marked powers of locomotion. No preparation will be necessary beyond mounting a thin layer of blood or other fluid.

2. Recklinghausen pointed out the resisting power of many of these organisms to alkalies and dilute acids: solutions of these were formerly used to clear away fatty and albuminoid particles, but now-a-days they are employed only as a part of complex staining processes.

3. **Staining.**—This is by far the most important method, and it is to Weigert that we owe the introduction of the reagents—the aniline dyes. Logwood stains many fungi well, but it has no preference for them over animal tissues, so it does not cause them to stand out. The aniline dyes most often used are fuchsine, methyl violet, and methylene blue, or Bismarck brown for photography; watery solutions are employed, from ½ to 5 per cent. Cover-glasses and slides should be cleaned in very dilute nitric acid and kept in alcohol; before use they should be heated in a spirit flame whilst held in forceps. Take two cover-glasses which have just cooled, place a *small* drop of the fluid on one, put the other glass on the top of it, squeeze the glasses gently together, and then glide one off the other, so as to leave a *very thin* layer of the fluid on each. Now dry both cover-glasses by passing them several times through a spirit flame. A temperature of 120° F. should be reached for a few minutes to produce insolubility and fixation to the glass of any albumen. If a weak staining solution is used, the glasses must be floated on it for some time; but a strong solution (2–5 per cent.) is sometimes as good, and stains deeply in less than a minute. Pour a little on to the glass, pour it off after a few seconds, and wash with distilled water from a wash-bottle; dry over a flame. Warm a slide, and just melt on it a little solid balsam; drop the slightly warmed cover-glass on to this and press it down.

For fluids rich in albumen a concentrated solution of aniline brown in glycerin and water (equal parts) may be used with advantage.

Certain organisms are distinguished by holding to basic aniline dyes, as fuchsine, gentian violet, methyl violet, etc., which they have taken up slowly from fluids which may be either alkaline or acid (Ziehl), when they are acted on by a solution of nitric acid (1 in 3), whilst everything else is decolorized, including other kinds of bacteria. These latter and the tissues may, after the acid has been washed off, be stained with some contrast-color—*e. g.* fuchsine and methylene blue. This method will be described under "Tissues." The chief fungi known to stain in this way are B. tuberculosis and B. lepræ; a coccus also has been met with. B. tuberculosis is now constantly sought for in pus, in sputum, and in urine for purposes of diagnosis or to learn the result of treatment.

For the examination of fluids for B. tuberculosis, Gibbes' double stain is the quickest, and is said to be as reliable as any (Vignal). It consists of two parts of fuchsine to one part of methylene blue dissolved in an alcoholic solution of aniline oil.

A method of very general use in the examination for bacteria, both of cover-glass specimens and of sections, has been introduced by Dr. Gram of Copenhagen. Cover-glasses are soaked for some minutes, sections for some hours, in Ehrlich's aniline-water solution of gentian or methyl violet until they are deeply stained. They are then placed on or in a solution of 1 part of iodine and 2 of potassic iodide in 300 of water until they turn brown (*i. e.* two or three minutes). Alcohol followed by oil of cloves is used to decolorize the specimen, which is then mounted. Most organisms remain deeply stained, but some—gonococcus and Friedländer's pneumococcus—are decolorized. Eosine or Bismarck brown may be used as a contrast stain.

Ehrlich's solution is made by adding a concentrated alcoholic solution of methyl or gentian violet to aniline-water (see below) until it becomes opalescent.

(*b*) **MICRO-ORGANISMS IN TISSUES.**—Tissues for examination should be placed in thin slices as soon as possible after death in strong methylated spirit or absolute alcohol. When thoroughly hardened very thin sections must be cut either by hand or by some microtome. If a freezing-machine is used a thinnish slice of the tissue must be soaked in plenty of water for two or three hours, and then put into mucilage (B. P.) for a similar time. The sections are to be placed for twelve hours or longer in a 1 per cent. watery solution of the dye selected, always filtered before use; warmth facilitates

staining. Some workers transfer the stained section to a 1 per cent. solution of glacial acetic acid, then to absolute alcohol, and finally to oil of cloves: others put them straight into alcohol. Each one of these fluids dissolves the dye out of the tissue, and the difficulty is to carry the sections through them rapidly enough. It is best, therefore, at first to take only one section at a time out of the staining fluid. One or two trials will show how long the section must be left in each fluid in order that it may still retain a rather pale color when it is spread out on the slide. Superfluous oil of cloves is now run off, and the section dried with a piece of clean filter-paper pressed firmly on it. A drop of Canada balsam dissolved in xylol is put on the cover-glass, and this is applied; chloroform and benzol balsam slowly dissolve out the stain, and pure balsam is rather difficult to work with.

If a blue or violet stain has been used, the sections, after washing in alcohol, may be dipped in water for a moment, and then placed in eosine or carmine solution for an hour; the tissue-elements acquire a red tint, whilst the organisms remain blue or violet. The sections must now be carried through alcohol and oil of cloves; then mounted.

To examine tissues for B. tuberculosis or B. lepræ, Ehrlich's process is the best. Many contrast stains may be used; we shall speak of fuchsine and methylene blue. To 100 c.c. of water add 4 c.c. of pure aniline (ordinary aniline is much cheaper and very good), shake well and filter; to the filtrate add 11 c.c. of a saturated alcoholic solution of fuchsine. Prepare also a saturated solution in absolute alcohol of methylene blue, and dilute nitric acid (B. P.) with two parts of water, or with three, if this decolorizes too quickly. Place the sections in the fuchsine solution for at least two hours in a warm place; then transfer them to the nitric-acid solution, and leave them until the color is almost gone; then rinse them in water and put them into methylene blue for an hour. Now pass them through absolute alcohol and oil of cloves, and mount as above. Either B. tuberculosis or lepræ will appear red on a blue ground; all other organisms present will be blue.

With large and delicate sections it is a good plan to use the glass slide as a section lifter, pushing it obliquely into the cloves or even the alcohol, and there spreading the section out upon it. Large vessels and plenty of the fluid must be used for this purpose.

With large organisms or with successful contrast-staining a power of five hundred diameters and ordinary illumination will be sufficient

for most purposes; but for the smaller fungi the highest powers made and a substage condenser of very wide angular aperture are necessary.[1]

CULTIVATION.—Having determined the presence of organisms in a fluid or tissue, it may be wished to cultivate them to study their life-conditions or to inoculate the pure organisms on other animals.

Three methods may be mentioned—cultivation in fluids, in solids, and in living animals.

In Fluids.—Klebs introduced a method which he called "Fractionirte Cultur." It consists in adding to a sterile-fluid a small quantity of a fluid or substance containing the fungus. Under suitable conditions the latter will grow. A small quantity of the culture-fluid may then be added to another flask, and so on until all vestiges of what was inoculated in the first flask along with the original organisms must have disappeared. If more than one kind of fungus is inoculated, or if in the inoculation of successive flasks contamination from the air or apparatus occurs, it may be impossible to obtain a pure cultivation of one organism.

In Solids.—Koch, therefore, introduced a solid culture-ground. Clear meat-broths and other fluids are peptonized, and have added to them sufficient gelatin (2½–3 per cent.) to render them solid at 20°–25° C., at which temperature most fungi will grow fairly. Klein, however, finds it necessary for the latter temperature to have at least 10 per cent. of gelatin present. Agar-agar, obtained from seaweed, is now used to thicken fluids required to remain solid at the temperature of the body and higher. Serum of blood solidified and sterilized by heating to 60° C. for short periods on consecutive days may be employed. A thin layer of the gelatin may be spread on a cover-glass; a recently-heated wire, having on it the material to be examined, is drawn across the gelatin in two or three lines, and the cover is inverted over a glass cell. Examination will now show what organisms are present, and where the one it is wished to grow is situate; the growth may be watched and fresh culture-grounds inoculated from it. As the inoculation takes place in air, organisms may fall upon the gelatin or the wire may catch one or two. The latter would lie in the inoculation-lines; the former would probably be away from them, and therefore at once recognizable. Examination of several lines guards against the former fallacy. "Plate" cultivations are now fre-

[1] Koch. *Traum. Inf. Dis.*, p. 27.

quently used. To examine air a glass plate covered with gelatin peptone may be exposed for a given time, then kept under a moist bell-jar: colonies will grow wherever germs have fallen, and any one can be cultivated in tubes. Again, earth or a tissue may be broken up in sterilized water, and a little of this may be shaken with sterilized gelatin peptone; the latter is then poured on a plate and allowed to set. Most frequently such cultivations are carried on in test-tubes, inoculated with a platinum wire heated to redness just before it is dipped into the substance to be examined. A puncture with it is then made into the gelatin. A very handy method of cultivation is the inoculation of slices of recently-boiled potato, made with a pure knife and kept under a bell-jar in moist air.

In Animals.—Koch injected fluids containing many kinds of organisms into the bodies of animals. In only one case did two organisms develop, and then whilst one (bacillus) was in the blood, the other (coccus) remained in tissues round the inoculation-puncture. The former gave rise to septicæmia, and could be easily inoculated alone; but the latter, which caused spreading gangrene, could not be obtained free from the bacillus until both were inoculated on an animal, in which the latter could not grow, whilst the former flourished. Pure cultivation of each could now be carried through any number of animals.[1] It may, however, be impossible to find an animal in which the organism it is desired to cultivate will grow.

In all such experiments apparatus must be purified at 150° C. for some hours, instruments passed through a flame before use, and so forth; they should be carried on in the purest and quietest atmosphere obtainable. The food-material, its reaction, the temperature, the amount of oxygen, must be varied experimentally to suit any fungus it is desired to grow.

[1] Koch, p. 43.

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